DEVELOPMENT AND APPLICATION OF

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（新規人工不斉補助剤の創製とその応用）

須藤　篤

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DEVELOPMENT AND APPLICATION OF NEW ARTIFICIAL CHIRAL AUXILIARIES

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by

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PREFACE

The studies presented in this thesis have been carried out under the direction of Professor Kazuhiko Saigo at the University of Tokyo during 1992-1997. The thesis is concerned with the development of new artificial chiral auxiliaries and their applications to asymmetric synthesis.

The author express his sincere gratitude to Professor Kazuhiko Saigo for his valuable guidance and encouragement throughout this work.

The author is grateful to Mr. Masao Nohara, Dr. Yukihiko Hashimoto, Dr. Akihiro Orita, Dr. Minoru Hayashi, and Dr. Kazushi Kimbara for helpful discussions. He also appreciates the collaboration of Mr. Kazuo Takaoki, Mr. Masaru Matsumoto, Mr. Kazutaka Seki, and Mr. Hiroaki Yoshida. The author extends his thanks to the Japan Scholarship Society for the scholarship to him.

Finally, the author wishes to express his hearty thanks to his parents for their affectionate encouragement.

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CHAPTER III. DEVELOPMENT AND APPLICATION OF *CIS*-2-AMINO-3,3-DIMETHYL-1-INDANOL

CHAPTER I. GENERAL INTRODUCTION

1. Importance of Chirality

Recognition events in biology almost always involve the chiral recognition of a biologically active molecule by a chiral, non-racemic receptor. The two enantiomers of a chiral drug cannot be expected to bind equally well to a receptor and to cause same biological responses, because the bioreceptor consists of chiral macromolecules such as nucleic acids, polysaccharides, and proteins, which are polymers of subunits with high optical purity.

There are many examples of pharmaceutical drugs, agrochemicals and other chemical compounds, of which the desired biological property is related to their absolute configuration (Fig. I-1). In the series of eight possible stereoisomers of 3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic esters (pyrethroid insecticides), deltamethrin is the most effective insecticide whereas its enantiomer is inactive. In the field of food additives, aspartame ((*S*,*S*)-isomer) is used as an artificial sweetener, whilst the (*S*,*R*)-form tastes bitter and must be avoided in the manufacturing process. In testing drugs for therapeutical application, it is often found that only one enantiomer possesses a desired biological activity. In the case of propanolol, the (*S*)-enantiomer is a β-blocker whilst the (*R*)-enantiomer possesses no activity. The (*S*)-enantiomer of ibuprophen is active as pain reliever whereas the (*R*)-enantiomer is inactive. (–)-Physostigmine is a natural product which is an inhibitor of the cortex acetylcholinesterase. This natural enantiomer is 700 times more potent *in vitro* than the unnatural enantiomer.

Furthermore, in some cases, even though an enantiomer is highly active as a drug, it is possible that the opposite enantiomer is not only inactive but also possesses a different activity and causes toxic side effects. Tragedy, which occurred in the 1960s after racemic thalidomide was administrated to pregnant women, is a well-known example. The (*R*)-enantiomer of thalidomide does exhibit desirable analgesic properties; the (*S*)-enantiomer does not, instead, is tetratogenetic and induces fetal malformation or death. In some cases, selective biotransformation of an inactive enantiomer can also produce a far different antagonist for a receptor. The (*R*)-isomer of deprenyl is an antidepressant and anti-Parkinson's disease drug,

however, the (*S*)-isomer is not only less active but also is converted into (*S*)-(+)-methamphetamine and (*S*)-(+)-amphetamine, which cause undesired nervous stimulation.

After the thalidomide-tragedy, in these days, the marketing regulations for synthetic drugs have become significantly more stringent. In order to commercialize a racemate, the activity of each enantiomer of the racemate must be carefully evaluated; commercialization is only permitted, if it can be shown that both enantiomers have similar potency or that the non-potent enantiomer causes no side effect. Even when the other enantiomer is inert, it may be desirable to prepare and use the active one in its pure form. For drug delivery, the relative potency of the use of only one active enantiomer is such that the dose can be reduced in half compared with the use of a racemate. Moreover, there is an economic reason; the production of the inert isomer represents a waste of starting materials and resources.

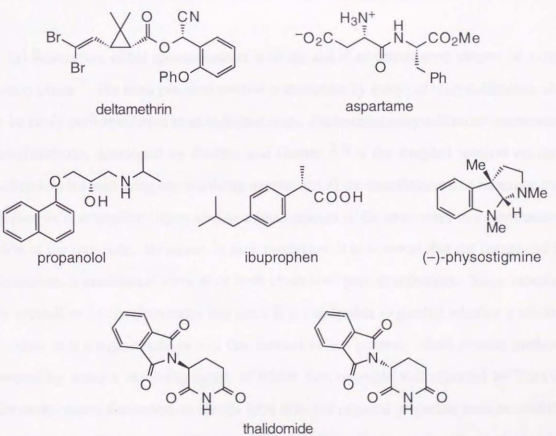


Figure I-1. Chiral Bioactive Compounds

2. Categories of Strategies in Order to Obtain Enantiopure Compounds

Under the circumstances mentioned in the previous section, many organic chemists concern themselves with developing various methods to obtain enantioenriched substances. These methods are categorized into three strategies as shown below.

Categories of Strategies in Order to Obtain Enantiopure Compounds

(a) resolution

- preferential crystallization
- resolution of racemates via their derivation into the corresponding diastereomers (salt, ester, complex, etc.)
- resolution by a chiral stationary phase (HPLC, etc.)

(b) kinetic resolution

(c) asymmetric synthesis

(a) Resolution, either spontaneous or with the aid of an enantiopure reagent or a chiral stationary phase:[1] The most practical method is resolution by means of recrystallization, since it can be easily performed even in an industrial scale. Preferential recrystallization (spontaneous recrystallization), developed by Pasteur and Gernez,[2,3] is the simplest method via direct crystallization without using any resolving agents; one of the enantiomers of a racemate could be preferentially crystallized upon seeding a small amount of the enantiomer to a supersaturated solution of the racemate. However, in such resolution, it is essential that the compound is a conglomerate, a mechanical mixture of both crystals of pure enantiomers. Since racemates rarely crystallize as conglomerates and since it is impossible to predict whether a substrate crystallizes as a conglomerate or not, this method is less general. More general method is performed by using a resolving agent, of which first example was reported by Pasteur.[4] Unlike enantiomers, diastereomers always have different physical properties such as solubility. This makes it possible to separate diastereomers physically. For example, when a racemic base was allowed to mix with an enantiomerically pure acid, a mixture of the corresponding diastereomeric salts is obtained. They can be separated by a simple recrystallization, if the

difference in solubility between them is large enough. The pure enantiomer of the base can be obtained by the decomposition of the separated salt.

(b) Kinetic resolution: Enzymes can recognize and transform a single enantiomer of a racemate, leaving the other enantiomer unchanged.[5] A chiral enantiopure reagent, which is used for asymmetric synthesis (*vide infra*) can also be used for kinetic resolution, when the reaction rates of the reagent with both enantiomers of a racemate are significantly different.[6]

(c) Asymmetric synthesis: Configuration concerning a chiral center, newly generated by the chemical transformation of a substrate, is regulated by internal chirality of the substrate and/or external chirality of a chiral reagent or medium. As mentioned in the previous section, since stereoselective preparation of a chiral compound is an important subject not only in the area of chemistry but also in human life, enormous kinds of asymmetric syntheses have been developed. The classification of asymmetric synthesis is given in the next section.

3. Classification of Asymmetric Synthesis

Asymmetric synthesis can be classified into three categories, as follows.[7]

Classification of Asymmetric Synthesis

1) Starting from a chiral substrate

$$A^{*}\text{ (chiral substrate)} + B\text{ (achiral substrate)} \longrightarrow A^{*}\text{–}B^{*}$$

2) Using a chiral template

$$A\text{ (achiral substrate)} \xrightarrow{+\,X^{*}\text{(chiral template)}} X^{*}\text{–}A\text{ (chiral substrate)}$$

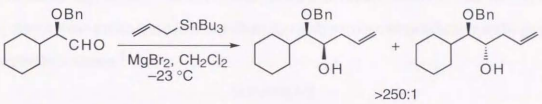
$$\xrightarrow{+\,B\text{ (achiral substrate)}} X^{*}\text{–}A^{*}\text{–}B^{*} \xrightarrow{-\,X^{*}} A^{*}\text{–}B^{*}$$

3) Using a chiral reagent

$$A\text{ (achiral substrate)} + B\text{ (achiral substrate)} \xrightarrow{\text{chiral reagent}} A\text{–}B^{*}\text{ or }A^{*}\text{–}B\text{ or }A^{*}\text{–}B^{*}$$

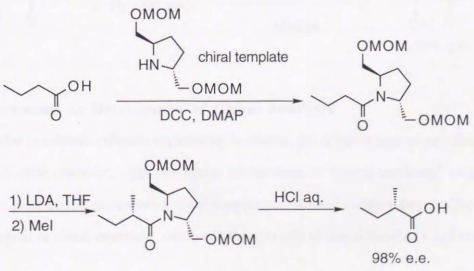
(a) Starting from a chiral substrate: A chiral substrate undergoes a highly stereoselective transformation leading to a desired enantiomeric target. In an example shown in Scheme I-1, the configuration of the newly created chiral center is effectively controlled by the chirality of the substrate.[8]

Scheme I-1



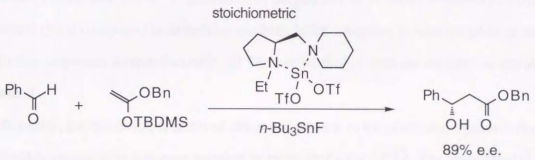
(b) Using a chiral template: A stoichiometric homochiral template is covalently attached to a substrate before chiral induction is performed. The chirality of the template controls the direction of the asymmetric induction, and the template is removed for reuse once upon the new chiral center is built. In this case, several steps are required in order to attach the template to the substrate and remove the template from the product. However, the product, which is covalently attached to the template, can be efficiently separated from its undesired diastereomeric isomer by classical methods such as recrystallization. In an example shown in Scheme I-2,[9] the target chiral carboxylic acid is stereoselectively synthesized via the diastereoselective alkylation of a chiral amide, which is prepared from the achiral carboxylic acid and the chiral template.

Scheme I-2

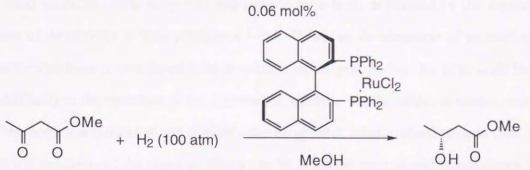


(c) Using a chiral reagent: Either a stoichiometric or a catalytic amount of a homochiral reagent is used in order to transform an achiral substrate to a chiral product or to connect several molecules giving a chiral product enantioselectively. In an example shown in Scheme I-3, the Sn(II) derivative, chirally modified with a homochiral diamine ligand, is used as a stoichiometric promoter in the enantioselective aldol condensation of the prochiral aldehyde with the ketene silyl acetal.[10] In an example shown in Scheme I-4, only a small amount of the chiral diphosphine-ruthenium complex efficiently catalyzes the enantioselective hydrogenation of the prochiral ketone.[11]

Scheme I-3



Scheme I-4



4. Requirements in Development of Chiral Auxiliary

In order to achieve efficient asymmetric synthesis, the development of an efficient chiral auxiliary is quite essential. The definition of the term of "chiral auxiliary" is sometimes ambiguous; generally, it represents a chiral template, however, in some cases, it also represents a chiral reagent or chiral molecule, which can be an origin of chiral templates and reagents. In

this thesis, the author defines the term of "chiral auxiliary" to indicate a chiral compound, which can be used as a precursor of chiral templates and/or chiral reagents.

An efficient chiral auxiliary must fulfill the following two important requirements: 1) Various kinds of chiral templates or chiral reagents, which are suitably designed for each asymmetric reactions can be easily derived from the auxiliary. 2) Both enantiomers of the auxiliary can be equally obtained by a simple operation.

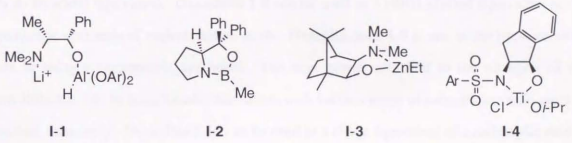
In general, a chiral auxiliary has been developed by means of selection and derivation of an appropriate natural chiral compound. However, as long as a natural chiral compound is used as a chiral auxiliary, some serious problems would be given in fulfillment of the requirements mentioned above: 1) Limitation in the possible or available structural modification of a natural chiral compound is sometimes an obstacle for designing a chiral template or reagent with further improved stereoselectivity. 2) The availability of both enantiomers is not always guaranteed.

Recently, the utilization of artificial chiral compounds as templates and ligands is drawing considerable attention as a cogent solution to these problems.[11-13] The binaphthyls[11] and ferrocene derivatives,[12] which can be obtained in both enantiomeric forms by means of their resolution and is able to be used as versatile auxiliaries, are most remarkable examples. Some of the other artificial chiral templates and ligands have been developed by the asymmetric syntheses of themselves or their precursors.[13a,b] However, development of an auxiliary by asymmetric synthesis is considered to be unsuitable for the preparation in a large scale because of the difficulty in the operation of the asymmetric reaction. Furthermore, in some cases, only one of the both enantiomers of the auxiliary can be in hand, when a chiral reagent used in the asymmetric synthesis of the target auxiliary can be available only in one enantiomeric form. Although several chiral templates and ligands have been developed by resolution only in a small scale,[13] they are not so versatile auxiliaries since they are designed so as to be effective for particular reactions, respectively.

5. Importance of Chiral Amino Alcohols in Asymmetric Synthesis

Among various kinds of chiral auxiliaries, chiral 1,2-amino alcohols play a quite important role in asymmetric synthesis.

An amino alcohol itself can be used as a modifier of various metal reagents (Fig. I-2). The chirally modified $LiAlH_4$ (**I-1**)[14] can be used as a stoichiometric reagent in the enantioselective reduction of ketones. Corey and his co-workers showed that a small amount of the oxazaborolidine (**I-2**) catalyzes the enantioselective reduction of ketones with borane.[15] The use of the organozinc reagent (**I-3**) modified by an amino alcohol is widely developed for the enantioselective alkylation of aldehydes.[16] The arylsulfonylamino alcohol incorporated in complex **I-4** can be used as a chiral modifier of various Lewis acids, which catalyzes the enantioselective Diels-Alder reaction.[17]

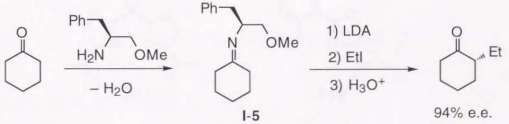


I-1 **I-2** **I-3** **I-4**

Figure I-2. Metal Complexes Modified With Chiral Amino Alcohols

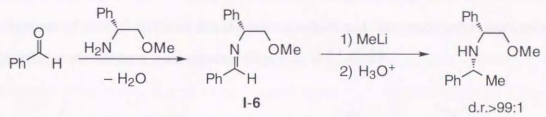
The chiral template, derived from an amino alcohol by its *O*-alkylation, is effectively used in the diastereoselective alkylation of the corresponding homochiral imine **I-5** (Scheme I-5)[18] and in the diastereoselective addition reaction of various organometallic reagents to the corresponding homochiral imine **I-6** (Scheme I-6).[19]

Scheme I-5



I-5 94% e.e.

Scheme I-6



Heterocycles derived from amino alcohols are widely used as quite reliable chiral templates (Fig. I-3).[20] Oxazolidine **I-7** is a useful substrate for a nucleophilic substitution; it acts as an acetal equivalent. Oxazinone **I-8** can be used as a chiral glycine equivalent in the asymmetric synthesis of various amino acids. Oxazolidinone **I-9** is one of the most versatile tools in today's asymmetric synthesis. The acyl group, attached to the nitrogen of the oxazolidinone, can be transformed into others with various kinds of substituents with good to excellent selectivity. Oxazoline **I-10** can be used as a chiral equivalent of a carboxylic acid in an asymmetric alkylation, conjugate addition, etc. It is also used as a template in an asymmetric aromatic coupling reaction to obtain axially chiral compounds. Recently, bis-oxazoline **I-11** and phosphine-oxazoline hybrid **I-12** have been reported to be versatile ligands for homogeneous transition metal-catalyzed systems.

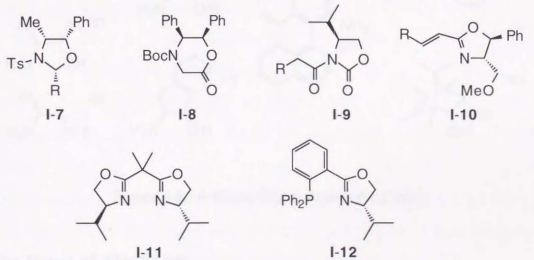


Figure I-3. Chiral Heterocycles Derived from Various Amino Alcohols

As can be seen from these examples, chiral 1,2-amino alcohols are usually derived from naturally occurring α-amino acids, alkaloids, and terpenes (Fig. I-4).[20] Recently, the development of several artificial chiral amino alcohols and their successful applications to asymmetric syntheses have been reported (Fig. I-5).[13,17,21-24]

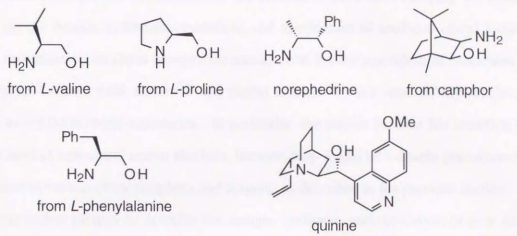


Figure I-4. Amino Alcohols Derived from Naturally Occurring Compounds

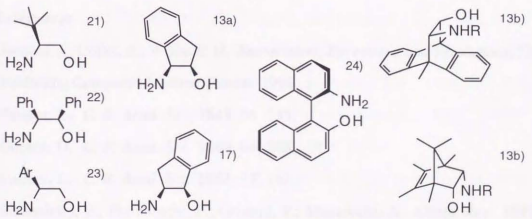


Figure I-5. Artificial Chiral Amino Alcohols

6. The Object of This Thesis

In order to obtain both enantiomers of an artificial chiral auxiliary, the resolution of the racemic target chiral auxiliary should be preferable to its asymmetric synthesis from the viewpoint of application in a large-scale operation. Furthermore, resolution should be

preferable to asymmetric synthesis, because complicated multi-step transformations can be avoided to minimize the loss of optically active target compounds. However, much trial-and-error is sometimes required in order to achieve resolution, and there are only a few successful reports on the resolution of artificial auxiliaries in a large scale by a simple operation. Taking into account these present circumstances, our laboratory have been carrying out systematic studies on the design, synthesis, resolution, and application of artificial chiral auxiliaries. During investigation on chiral recognition mechanisms for the resolution of racemates in our laboratory,[25] some chiral amines[26] and amino alcohol[22] were successfully resolved, and applied as artificial chiral auxiliaries. In particular, the author focused his attention on the development of new chiral amino alcohols, because they would be valuable precursors for the preparation of various chiral templates and reagents as described in the previous section. In this thesis, the author intends to describe the design, synthesis, and resolution of new artificial chiral amino alcohols, *cis*-2-amino-1-acenaphthenol and *cis*-2-amino-3,3-dimethyl-1-indanol, and their applications to various kinds of asymmetric syntheses.

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CHAPTER II. DEVELOPMENT AND APPLICATION OF *CIS*-2-AMINO-1-ACENAPHTHENOL

Section I. Design, Synthesis, and Resolution of *cis*-2-Amino-1-acenaphthenol

1. Introduction

Since chiral amino alcohols are one of the most important classes of chiral auxiliaries, development of novel amino alcohols has been drawing significant attention in the area of asymmetric synthesis.[1] During the investigation on chiral recognition mechanisms for the resolutions of racemates in our laboratory,[2] artificial chiral amino alcohol, *erythro*-2-amino-1,2-diphenylethanol (**II-1**), was found to be quite efficiently resolved in a large scale by preferential crystallization without any resolving agent.[3] Furthermore, this amino alcohol is a quite useful chiral auxiliary in asymmetric synthesis such as the diastereoselective alkylation reaction of the corresponding imines.[4] The author intended to design new artificial chiral amino alcohols, which are more useful chiral auxiliaries than **II-1**. As a method to obtain homochiral amino alcohols thus designed, the author focused his attention to the synthesis of their racemates and their resolution, because resolution should be preferable to asymmetric synthesis from the viewpoints of simplicity and ease of a large-scale operation.

In this section, the author describes the design, synthesis, and resolution of a new artificial chiral amino alcohol, *cis*-2-amino-1-acenaphthenol.

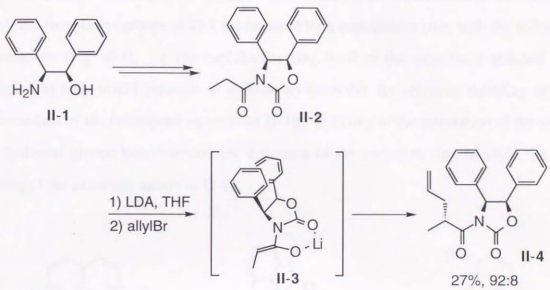
2. Results and Discussion

2.1. Design of *cis*-2-Amino-1-acenaphthenol and Its Analogues

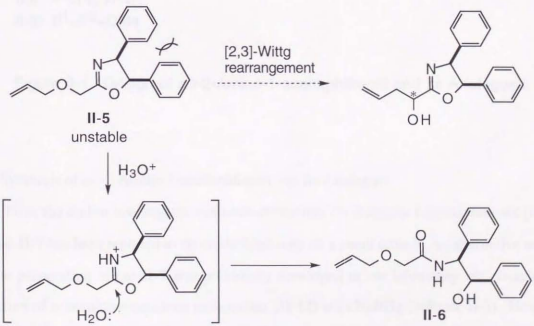
During the investigation on application of **II-1** to asymmetric synthesis, the diastereoselective alkylation reaction of the *N*-propionyloxazolidinone **II-2** derived from **II-1** was examined (Scheme II-1). When the lithium enolate of **II-2** was allowed to react with allyl bromide, the diastereoselectivity was somewhat low (d.r.=92:8). This low diastereoselectivity was considered to arise from insufficient shielding of one side of the molecule **II-3** by the phenyl ring attached to the carbon atom adjacent to the nitrogen atom, because the two phenyl

groups are obliged to be parallel to each other to avoid serious steric repulsion between their *ortho* hydrogens.

Scheme II-1



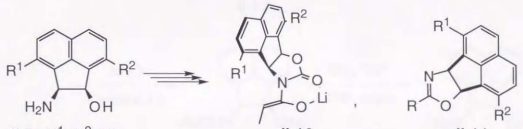
Scheme II-2



The author also tried to synthesize 2-(allyloxymethyl)oxazoline **II-5** in order to carry out the diastereoselective [2,3]-Wittig rearrangement of **II-5** (Scheme II-2).[5] However, the oxazoline moiety of **II-5** decomposed during the purification by silica gel chromatography to

give the corresponding amide **II-6**, which was supposed to be formed by hydrolysis of the oxazoline moiety. This low stability of the oxazoline derivative was considered to arise from the distortion of the oxazoline ring caused by steric repulsion between the two phenyl ring.

The author then designed several comformationally rigid amino alcohols **II-7**~**II-9**, in which the two phenyl groups of **II-1** are replaced by a naphthalene ring, with the following expectations (Fig. II-1): 1) The naphthalene ring itself or the substituent attached to a naphthalene ring would protrude in a direction favorable for efficient shielding of one diastereoface of the corresponding enolates **II-10**. 2) Fixing of the orientation of the amino and hydroxyl groups would release the distortion of the oxazoline ring to avoid the ring opening of the oxazoline moiety of **II-11**.



II-7: $R^1=R^2=H$
II-8: $R^1=Ph$, $R^2=H$
II-9: $R^1=R^2=OMe$

II-10 , **II-11**

Figure II-1. Design of *cis*-2-Amino-1-acenaphthenol and Its Analogues

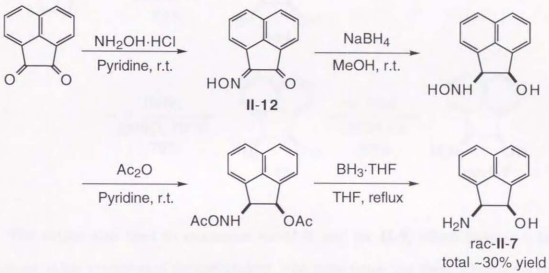
2.2. Synthesis of *cis*-2-Amino-1-acenaphthenol and Its Analogues

First, the author investigated synthesis of racemic *cis*-2-amino-1-acenaphthenol (rac-**II-7**). rac-**II-7** has been reported to be synthesized only on a small scale.[6] An alternative method for the preparation of rac-**II-7** was previously developed in our laboratory via *cis*-selective reduction of acenaphthenequinone monooxime (**II-12**) with $NaBH_4$ (Scheme II-3). However, the overall yield for this sequence was low, and the *cis*-selectivity for the reduction of **II-12** was sometimes lowered by small change of the reaction conditions.

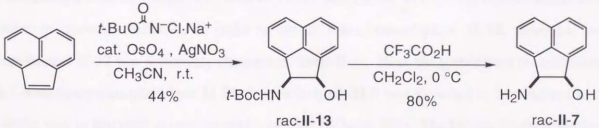
A new route for the synthesis of rac-**II-7** was achieved by using the *cis*-hydroxyamination protocol developed by Sharpless and his co-workers,[7] which gave rac-**II-7** via only two steps starting from acenaphthylene: Treatment of acenaphthylene with a catalytic

amount of osmium tetroxide, 1.5 eq. *t*-butyl *N*-chloro-*N*-sodiocarbamate, and 3.0 eq. silver nitrate in acetonitrile gave racemic *cis*-Boc-amino alcohol rac-**II-13** in 44% yield (Scheme II-4). No *trans*-product was detected. Deprotection of *N*-Boc group of rac-**II-13** with 50% trifluoroacetic acid in dichloromethane at 0 °C afforded rac-**II-7** in 80% yield. This method was very straightforward and allowed to prepare 0.5-1 g of rac-**II-7** in each run.

Scheme II-3



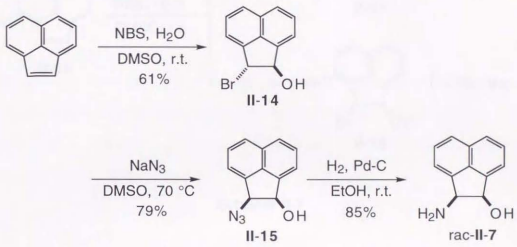
Scheme II-4



Although this route provided rac-**II-7** quite easily, the expensive and toxic osmium tetroxide were considered to prohibit a large scale operation, then, an alternative method for a large scale preparation of rac-**II-7** was tried to develop. Finally, rac-**II-7** was prepared via hydroxyhalogenation followed by azidation and reduction (Scheme II-5):[8] Acenaphthylene was converted to racemic *trans*-bromohydrin **II-14** by the reaction with *N*-bromosuccinimide and water in dimethyl sulfoxide. **II-14** was converted to racemic *cis*-azido alcohol **II-15** by

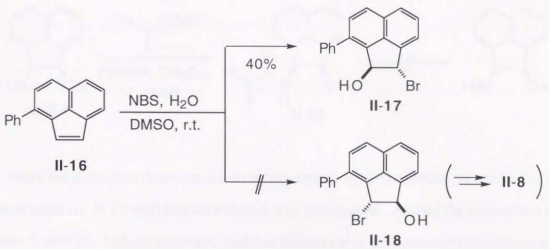
treatment with sodium azide, and hydrogenation (catalytic Pd/C, H_2, EtOH) of **II-15** gave racemic *cis*-amino alcohol rac-**II-7** in 41% overall yield. This route provided a large amount of rac-**II-7** without the need for complete purification in each step.

Scheme II-5



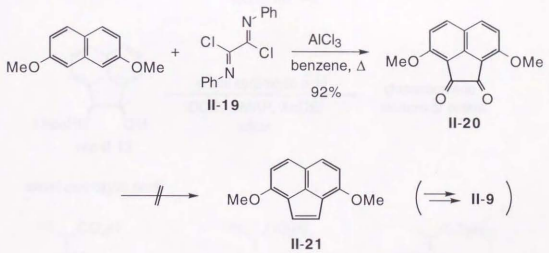
The author also tried to synthesize rac-**II-8**, and rac-**II-9**, which possess a larger substituent at the 7-position of the naphthalene, with expectation that these substituents would more effectively influence the chiral environment near to the stereogenic center adjacent to the nitrogen atom. 2-Phenylacenaphthylene (**II-16**), which was synthesized from 2-nitroacenaphthene in 3 steps (20% overall yield), was treated with *N*-bromosuccinimide and water in dimethyl sulfoxide in order to obtain *trans*-bromohydrin **II-18**, however, its regioisomer **II-17** was selectively obtained (Scheme II-6). Next, the author tried to synthesize 2,7-dimethoxyacenaphthylene **II-21**, from which rac-**II-9** was expected to be obtained in a similar way to that used in order to obtain rac-**II-7** (Scheme II-7). The Friedel-Crafts acylation of 2,7-dimethoxynaphthalene with **II-19** gave 2,7-dimethoxyacenaphthenequinone **II-20** quite easily.[9] However, several attempts to synthesize **II-21** from **II-20** by means of usual reductive methods were resulted in failure. These results made the author to give up the synthesis of **II-8** and **II-9**.

Scheme II-6



II-16 II-17 II-18

Scheme II-7

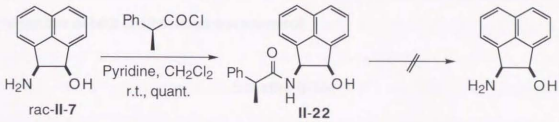


II-19 II-20 II-21

2.3. Resolution of *cis*-2-Amino-1-acenaphthenol via Its Diastereomeric Esters

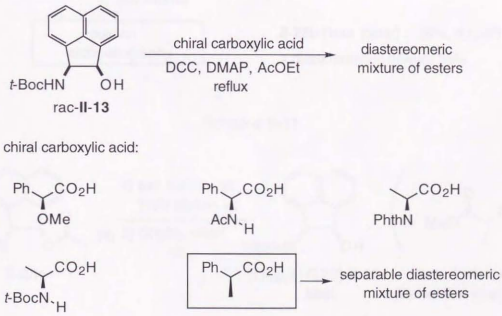
With racemic *cis*-2-amino-1-acenaphthenol rac-**II-7** in hand, the resolution of rac-**II-7** was investigated. *N*-Acylation with (*S*)-2-phenylpropionyl chloride gave an easily separable diastereomeric mixture of the corresponding amides **II-22** (Scheme II-8). However, the hydrolysis of the amide bond under acidic conditions led to decomposition. Other deacylations, such as *O*-alkylation by the Meerwein's reagent followed by hydrolysis and the half-reduction of the amide function, also resulted in failure.

Scheme II-8



Next, the resolution via esters, which were prepared by the condensation reaction of Boc-amino alcohol rac-**II-13** with homochiral acid, was investigated. Among the homochiral acids examined, only (*S*)-2-phenylpropionic acid was found to give a chromatographically separable diastereomeric mixture (Scheme II-9).

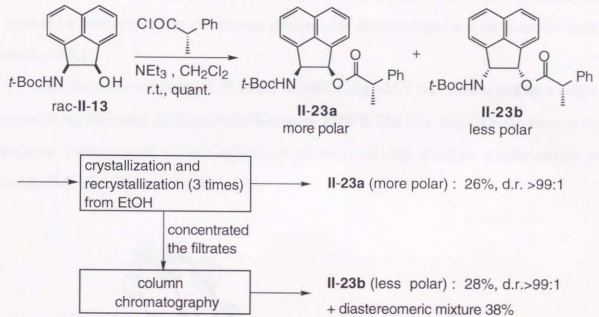
Scheme II-9



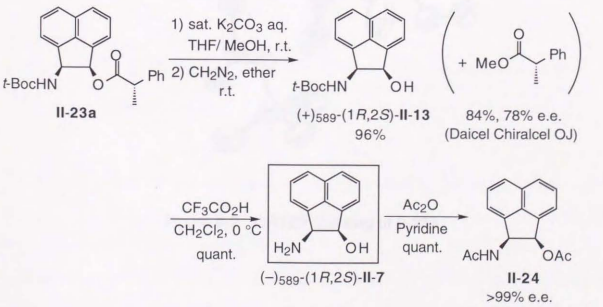
Acylation of rac-**II-13** with homochiral (*S*)-2-phenylpropionyl chloride under mild conditions gave a diastereomeric mixture of esters **II-23a** and **II-23b** in quantitative yield (Scheme II-10). Although this mixture was separable by chromatography, it was found that the combination of recrystallization and column chromatography was most practical. Crystallization and recrystallization 3 times of a diastereomeric mixture of **II-23a** and **II-23b**

from ethanol gave the more polar (less soluble) diastereomer **II-23a** in 26% yield with >99:1 diastereomeric ratio. Separation of the concentrated filtrate by flash column chromatography gave the less polar diastereomer **II-23b** in 28% yield with >99:1 diastereomeric ratio and 38% of the mixture of both diastereomers was recovered.

Scheme II-10



Scheme II-11



Each homochiral Boc-amino alcohol **II-13** was liberated by treatment of the highly pure diastereomer with a saturated aqueous potassium carbonate solution (Scheme II-11). The Boc group was removed with trifluoroacetic acid to afford optically active **II-7** in quantitative yield. The enantiomeric purity was confirmed on the basis of chiral HPLC analysis of the corresponding *N*,*O*-diacetylated products **II-24** for both enantiomers. The analysis revealed that (–)589-**II-7** obtained from **II-23a** (d.r.>99:1) was >99% e.e. without any racemization nor epimerization. However, recovered methyl 2-phenylpropionate (84% yield), which was obtained by treatment of a crude reaction mixture with diazomethane, was racemized to some extent (78% e.e.).

The absolute configuration of amino alcohol (–)589-**II-7** was determined by a single-crystal X-ray structural analysis of diastereomeric ester **II-23a** (Fig. II-2). On the basis of the absolute configuration of (*S*)-2-phenylpropionic acid, the absolute configuration of (–)589-**II-7** was determined to be 1*R*,2*S*.

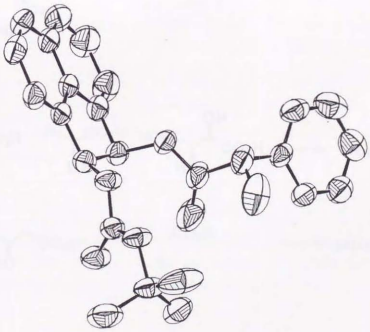
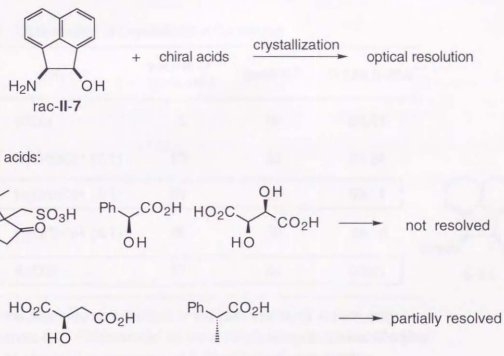


Figure II-2. ORTEP Drawing of **II-23a**

2.4. Resolution of *cis*-2-Amino-1-acenaphthenol via Its Diastereomeric Salts

Although the resolution of rac-**II-7** via its corresponding diastereomeric Boc-amino esters provided both optically pure enantiomers of **II-7**, this resolution method requires several protection and deprotection steps and therefore a more facile and practical method was desired. Then, the author examined the resolution of rac-**II-7** via diastereomeric salts with several kinds of chiral acids, such as camphorsulfonic acid, mandelic acid, tartaric acid, malic acid, and 2-phenylpropionic acid; the diastereomeric salts were recrystallized from water, ethanol, or their mixture. Among the resolving agents examined, 2-phenylpropionic acid was the most effective (Scheme II-12).

Scheme II-12



Examination of several conditions for recrystallization (Scheme II-13, Table II-1) revealed that diastereomeric salt **II-25a** was preferentially crystallized when a 2:1 mixture of water and ethanol was used as a solvent (entry 2). With using a larger amount of solvent (entry 3), **II-25a** was obtained in 37% yield with excellent selectivity (d.r.=99:1). On the other hand, crystallization of a mixture of the diastereomeric salts from ethyl acetate gave the opposite diastereomer **II-25b** predominantly (entry 5).

Scheme II-13

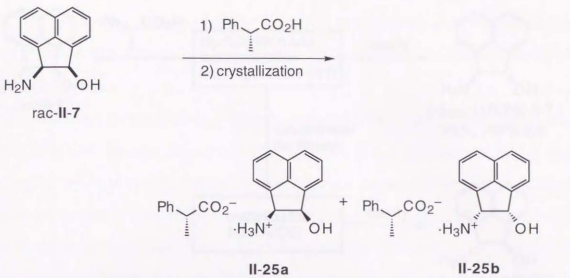
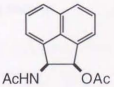


Table II-1. Optimization of Crystallization Conditions

entry	solvent	volume of solv./ml [a]	yield/% [b]	**II-25a**:**II-25b** [c]
1	EtOH	5	18	56:44
2	H_2O/EtOH (2/1)	10	52	66:34
3	H_2O/EtOH (2/1)	20	37	99: 1
4	H_2O/EtOH (4/1)	25	30	94: 6
5	AcOEt	17	81	39:61

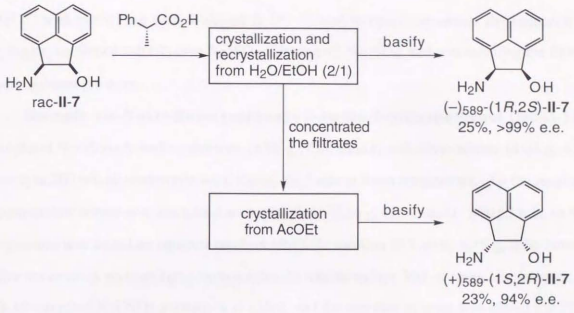


II-24

[a] 0.5 g of the diastereomeric mixture of the salts was used in each entry. [b] Based on rac-**II-7**. [c] Determined by chiral HPLC analysis (Daicel Chiralcel OD) of **II-24** obtained by treatment of **II-25** with Ac_2O and pyridine.

Thus, upon combining the two recrystallization processes using two different kinds of solvents, both enantiomers of **II-7** became available very efficiently (Scheme II-14). In this resolution, 2-phenylpropionic acid could be recovered almost quantitatively from each diastereomeric salt.

Scheme II-14



In conclusion, an artificial chiral amino alcohol, *cis*-2-amino-1-acenaphthenol (**II-7**) was designed, synthesized, and resolved. Racemic **II-7** was steroselectively synthesized via *trans*-bromohydrin derived from acenaphthylene. Both enantiomers of **II-7** was easily obtained by the resolution of **II-7** using homochiral 2-phenylpropionic acid as a resolving reagent.

3. Experimental

General Methods.

The melting points are uncorrected. HPLC analysis was performed with detection by UV light. ^{1}H-NMR (400 MHz or 270 MHz) spectra were measured with Me_4Si as an internal standard; the δ and J values are given in ppm and Hz, respectively. The unit for the values of IR spectra is cm^{-1}. The low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV on a Shimadzu QP-2000 and a JEOL JMS-AX505H, respectively. The X-ray crystal structure analysis was carried out by intensity measurement on a MAC Science MXC18 four-circle diffractometer, and structural solution and refinement by CRYSTAN.

All of the solvents were dried over sodium wire or molecular sieves, and were distilled before use. All the other reagents and solvents were purified according to standard convention. Reaction flasks were flame-dried under a stream of argon. All moisture- and oxygen-sensitive

reactions were conducted under an Ar atmosphere. The column chromatography was performed with E. Merck silica gel 60 (70-230 or 230-400 mesh). The preparative TLC (PTLC) was carried out with Wakogel B-5F. "Usual workup" represents the sequence of drying the combined extracts over Na_2SO_4, filtering off Na_2SO_4, and concentrating the filtrate under reduced pressure.

Racemic *cis*-*N*-*tert*-Butoxycarbonyl-2-amino-1-acenaphthenol (rac-**II-13**). *tert*-Butyl *N*-chloro-*N*-sodiocarbamate (4.09 g, 23.6 mmol) and silver nitrate (8.03 g, 43.2 mmol) in 200 mL of acetonitrile were stirred for 5 min at room temperature. To the resulting cream-yellow suspension was added acenaphthylene (2.34 g, 15.7 mmol). After 5 min, to this suspension was added an aqueous osmium tetroxide solution (2.7 wt%, 4.15 g, 0.66 mmol). After the reaction mixture (gray-brown colored) was stirred for 20 h at room temperature, 30 mL of saturated $NaHSO_3$ solution was added, and the reaction mixture was stirred for 12 h. After evaporation of acetonitrile, the product was extracted with AcOEt (100 mL × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction product was purified by short column chromatography (silica gel 60, 70-230 mesh, CH_2Cl_2) and recrystallization (hexane:benzene 1:1, 200 ml) to give rac-**II-13** (1.96 g, 6.78 mmol, 44%) as a white solid: Mp 156.7-157.5 °C; IR (KBr) 3430, 2990, 2880, 1695, 1520, 1180, 1170, 785; ^{1}H-NMR (270 MHz; $CDCl_3$) 1.51 (9H, s), 2.56 (1H, br d), 5.24 (1H, br d), 5.50 (1H, dd, *J*=5.9, 7.9), 5.60 (1H, dd, *J*=5.9, 6.1), 7.47-79 (6H, m). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.52; H, 6.74; N, 5.00.

Racemic *cis*-2-Amino-1-acenaphthenol (rac-**II-7**).

Method A: To a solution of **rac-II-13** (1.95 g, 6.83 mmol) in dichloromethane (50 mL) was added 50 mL of trifluoroacetic acid at 0 °C. After being stirred for 2 h, the reaction mixture was poured into 300 mL of 3 M KOH solution. The layers were separated, and aqueous layer was extracted with dichloromethane (50 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to give rac-**II-7** (1.01 g, 5.45 mmol, 85%) as a white solid, which immediately turns to a greenish amorphous mass under air: ^{1}H-NMR (60 MHz; DMSO-d6) 3.3 (3H, br s), 4.6 (1H, d, *J*=6.0), 5.2 (1H, d, *J*=6.0). Further purification and spectral data acquisition were carried out after derivation into its cinnamic acid salt (a white solid): Mp 158.7-159.2 °C; IR (KBr)

3450, 1640, 1562, 1550, 1390, 780, 720, 690; ^{1}H-NMR (270 MHz; $CDCl_3$+DMSO-d6) 4.50 (4H, br s), 4.87 (1H, br d, *J*=6.0), 5.63 (1H, d, *J*=6.3), 6.45 (1H, d, *J*=15.8), 7.47-79 (12H, m). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.57; H, 5.76; N, 4.18.

Method B: To a solution of acenaphthylene (1.00 g, 6.57 mmol) in 20 mL of dimethyl sulfoxide and 0.3 mL of water was added and *N*-bromosuccinimide (2.34 g, 13.4 mmol) in one portion under Ar at 0 °C. Upon removal of the ice-bath, the reaction temperature rose to ca. 60 °C. After stirring for 20 min at room temperature, the orange- colored reaction mixture was poured into 200 mL of cold water and extracted with ether (100 mL × 3). Evaporation of the solvent and short column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 95:5) gave 1.00 g of crude racemic *trans*-bromohydrin rac-**II-14** as a viscous brown oil: ^{1}H-NMR (60 MHz; $CDCl_3$) 2.6 (1H, br s), 5.5 (1H, d, *J*=2.0), 5.9 (1H, d, *J*=2.0), 7.5-7.9 (6H, m). To a solution of this crude rac-**II-14** in 50 mL of dimethylsulfoxide was added sodium azide (1.3 g, 20 mmol). The reaction mixture was stirred at 70 °C for 30 min, poured into 300 mL of cold water, and extracted with ether (100 mL × 3). The combined extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvent gave 670 mg of crude racemic *cis*-azido alcohol rac-**II-15** as a pale yellow crystal: ^{1}H-NMR (60 MHz; $CDCl_3$) 2.9 (1H, d, *J*=8.0), 5.1 (1H, d, *J*=8.0), 5.6 (1H, dd, *J*=7.0, 8.0), 7.5-8.0 (6H, m). This crude rac-**4** was dissolved in 50 mL of ethanol, and palladium-charcoal (5%, 0.15g) was added to the solution. The reaction mixture was stirred under a hydrogen atmosphere for 12 h, and the catalyst was filtered off. Evaporation of ethanol gave 500 mg of rac-**II-7** (2.70 mmol, 41% from acenaphthylene).

Optical Resolution of rac-**II-13.** To a solution of rac-**II-13** (1.72 g, 6.03 mmol) and 1 mL of pyridine in dichloromethane (80 mL), was added a solution of (*S*)-2-phenylpropionyl chloride in dichloromethane (20 mL) drop by drop over a period of 5 min under Ar at 0 °C. After being stirred for 1 h at 0 °C, saturated $NaHCO_3$ solution (20 mL) was added, and the reaction mixture was extracted with dichloromethane (20 mL × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction product was purified by column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 10:1) to give 2.41 g (6.03 mmol, 100%) of a diastereomeric mixture of

esters **II-23a** and **II-23b** as a white solid. Recrystallization of this diastereomeric mixture (764 mg, 2.68 mmol) from 7.5 mL of ethanol 4 times gave 198 mg (0.694 mmol, 26%) of more polar (less soluble) ester **II-23a** (d.r.>99:1) as colorless needles. Separation of the concentrated filtrate by flash column chromatography (silica gel 60, 230-400 mesh, hexane:AcOEt 30:1) gave 215 mg (0.754 mmol, 28%) of less polar diastereomer **II-23b** (d.r.>99:1) and a mixture of both diastereomers (38%). The diastereomeric purities of both **II-23a** and **II-23b** were determined by HPLC analysis (Merck LiChrosphere, hexane:AcOEt 10:1, α 1.17).

(1*R*,2*S*)-*N*-*tert*-Butoxycarbonyl-2-amino-1-acenaphthenyl (*S*)-2-phenyl -propionate (II-23a). Mp 163.5-163.8 °C; $[\alpha]^{21.6}_{589}$ –107.7 (c 1.50, $CHCl_3$); ^{1}H-NMR (270 MHz; $CDCl_3$) 1.50 (9H, s), 1.53 (3H, d, *J*=5.5), 3.77(3H, d, *J*=5.5), 4.97 (1H, d, *J*=9.5), 5.82 (1H, dd, *J*=7.6, 9.5), 6.61 (1H, d, *J*=7.6), 7.20-80 (11H, m); IR (KBr) 3450, 2980, 1730, 1695, 1510, 1245, 1150, 770, 695. Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.91; H, 6.60; N, 3.45.

(1*S*,2*R*)-*N*-*tert*-Butoxycarbonyl-2-amino-1-acenaphthenyl (*S*)-2-phenyl -propionate (II-23b). Mp 122.7-123.3 °C; $[\alpha]^{21.2}_{589}$ +89.9 (c 1.50, $CHCl_3$); ^{1}H-NMR (270 MHz; $CDCl_3$) 1.48 (9H, s), 1.51 (3H, d, *J*=5.9), 3.68 (3H, d, *J*=5.9), 4.81 (1H, d, *J*=8.4), 5.81 (1H, dd, *J*=7.6, 8.4), 6.59 (1H, d, *J*=7.6), 7.22-82 (11H, m); IR (KBr) 3450, 2980, 1732, 1695, 1520, 1250, 1180, 780, 700. Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.84; H, 6.53; N, 3.60.

(1*R*,2*S*)-(+)$_{589}$-II-13. To a solution of **II-23a** (375.5 mg, 0.899 mmol) in THF (4 mL) and methanol (4 ml) was added 4 mL of saturated K_2CO_3 solution at room temperature, and the suspension was vigorously stirred at room temperature for 2 h. The reaction mixture was acidified with 100 mL of 3 M HCl and extracted with dichloromethane (30 mL × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining residue was dissolved in ether (20 mL) and treated with excess amount of diazomethane (ether solution). Evaporation of ether, followed by column chromatography (silica gel 60, 70-230 mesh, hexane:dichloromethane 1:2), gave methyl (*S*)-2-phenylpropionate (123.6 mg, 0.753 mmol, 84%), of which the optical purity was determined to be 77.9% e.e. by chiral HPLC (Dicel Chiralcel OJ, hexane:2-propanol 9:1, α 1.20) and (1*R*,2*S*)-(+)$_{589}$-**II-**

13 (251.8 mg, 0.882 mmol, 99%): Mp 167.0-167.5 °C; $[\alpha]^{22.8}_{589}$ +12.3 (c 1.55, $CHCl_3$). The other spectral data were identical with those of rac-**II-13**.

(1*S*,2*R*)-(−)589-II-13. Treatment of **II-23b** (100.2 mg, 0.240 mmol) by a similar procedure described for (1*R*,2*S*)-(+)589-**II-13** yielded 64.3 mg (0.225 mmol, 94%) of (1*S*,2*R*)-(−)589-**II-13**: Mp 167.0-167.5 °C; $[\alpha]^{22.8}_{589}$ −12.3 (c 1.50, $CHCl_3$). The other spectral data were identical with those of rac-**II-13**.

(1*R*,2*S*)-(−)589-II-7. To a solution of (1*R*,2*S*)-(+)589-**II-13** (116.3 mg, 0.408 mmol) in dichloromethane (5 mL) was added 5 mL of trifluoroacetic acid at 0 °C. After being stirred for 2 h, the reaction mixture was poured into 30 mL of 3 M KOH, and the solution was extracted with dichloromethane (10 mL × 3). The combined extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to give (1*R*,2*S*)-(−)589-**II-7** (75.5 g, 0.408 mmol, 100%); $[\alpha]^{17.6}_{589}$ −26.8 (c 2.10, MeOH). Further purification and spectral data acquisition were carried out after derivation into its cinnamic acid salt: Mp 165.8-166.3 °C; $[\alpha]^{22.0}_{589}$ +7.4 (c 1.00, MeOH). The other spectral data were identical with those of the cinnamic acid salt of rac-**II-7**. Obtained (1*R*,2*S*)-(−)589-**II-7** was converted into its *N*,*O*-diacetylated derivative **II-24** by treatment with pyridine and acetic anhydride at room temperature, of which enantiomeric purity was determined to be >99% e.e. by chiral HPLC (Dicel Chiralcel OD, hexane:2-propanol 9:1, α 1.69, lower *Rf*).

(1*S*,2*R*)-(+)589-II-7. Treatment of (1*S*,2*R*)-(−)589-**II-13** (73.1 mg, 0.256 mmol) by a similar procedure described for the preparation of (1*R*,2*S*)-(−)589-**II-7** yielded 44.0 mg (0.238 mmol, 93%) of (1*S*,2*R*)-(+)589-**II-7**: $[\alpha]^{18.0}_{589}$ +24.3 (c 1.00, MeOH). Further purification and spectral data acquisition were carried out after derivation into its cinnamic acid salt: Mp 165.8-166.4 °C; $[\alpha]^{22.0}_{589}$ −7.4 (c 1.00, MeOH). The other spectral data were identical with those of the cinnamic acid salt of rac-**II-7**. Obtained (1*S*,2*R*)-(+)589-**II-7** was converted into its *N*,*O*-diacetylated derivative **II-24** by treatment with pyridine and acetic anhydride at room temperature, whose enantiomeric purity was determined to be >99% e.e. by chiral HPLC (Dicel Chiralcel OD, hexane:2-propanol 9:1, α 1.69, higher *Rf*).

Optical Resolition of rac-II-7

(1*R*,2*S*)-(–)589-II-7·(*R*)-2-phenylpropionic acid salt (II-25a). To a solution of rac-**II-7** (3.9 g, 21 mmol) in ethanol (10 mL) was added (*R*)-2-phenylpropionic acid (3.1 g, 21 mmol). The solvent was evaporated under reduced pressure to give the diastereomeric salt mixture (7.0 g, 21 mmol). The diastereomeric salt mixture was added water (160 mL) and ethanol (80 mL), and the suspension was refluxed to dissolve the diastereomeric salt mixture completely. The clear solution was allowed to stand at rt for 1.5 h (from the point when the precipitation started). The precipitate was collected by filtration. Recrystallization of the precipitate from water (106 ml) and ethanol (53 mL) under similar conditions gave diastereomerically pure **II-25a** (1.9 g, 5.7 mmol, 27% based on rac-**II-7** used) as pale yellow needles: $[\alpha]^{21.0}_{589}$ +3.42 (*c* 1.00, MeOH); mp 139-140 °C; IR (KBr) 3450, 1580, 1530, 1400, 780; ^{1}H-NMR (DMSO-d6) δ 1.3 (3H, d, *J*=6.9), 3.5 (1H, q, *J*=7.2), 4.8 (1H, d, *J*=7.2), 5.5 (1H, d, *J*=6.3), 7.2-7.3 (6H, m), 7.3-7.8 (5H, m).

(1*R*,2*S*)-(–)589-II-7. To a stirred suspension of **II-25a** (0.20 g, 0.60 mmol) in CH_2Cl_2 (30 mL) was added 1 M NaOH aq. (50 mL). The mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). Usual workup of the combined organic layer and extracts gave (1*R*,2*S*)-(–)589-**II-7** (0.10 g, 0.54 mmol, 91%). Obtained (1*R*,2*S*)-(–)589-**II-7** was converted into its *N*,*O*-diacetylated derivative **II-24** by treatment with pyridine and acetic anhydride at room temperature, of which enantiomeric purity was determined to be >99% e.e. by chiral HPLC (Dicel Chiralcel OD, hexane:2-propanol 9:1, α 1.69, lower *Rf*).

(1*S*,2*R*)-(+)589-II-7·(*R*)-2-phenylpropionic acid salt (II-25b). The combined filtrates of the crystallization and recrystallization performed in order to obtain **II-25a**, were concentrated under reduced pressure to give a solid mass (4.8 g). Crystallization of this salt mixture from ethyl acetate (450 mL) gave diastereomerically pure **II-25b** (1.8 g, 5.4 mmol, 27% based on rac-**II-7** used) as colorless needles: $[\alpha]^{21.0}_{589}$ –16.6 (*c* 1.00, MeOH); mp 144-147 °C; IR (KBr) 3000, 1600, 1560, 1400, 780; ^{1}H-NMR (DMSO-d6) δ 1.3 (3H, d, *J*=7.3), 3.5 (1H, q, *J*=7.3), 4.8 (1H, d, *J*=6.2), 5.5 (1H, d, *J*=6.3), 7.2-7.3 (6H, m), 7.5-7.8 (5H, m).

(1*S*,2*R*)-(+)589-II-7. According to the procedure given for the preparation of (1*R*,2*S*)-(–)589-**II-7**, (1*S*,2*R*)-(+)589-**II-7** (96 mg, 0.52 mmol, 87%) was obtained from **II-25b** (0.20 g, 0.60 mmol). Obtained (1*S*,2*R*)-(+)589-**II-7** was converted into its *N*,*O*-diacetylated derivative **II-24** by treatment with pyridine and acetic anhydride at room temperature, of which enantiomeric purity was determined to be 94% e.e. by chiral HPLC (Dicel Chiralcel OD, hexane:2-propanol 9:1, α 1.69, higher *Rf*).

Details for X-ray structural analysis of (1*R*,2*S*)-*N*-*tert*-Butoxycarbonyl-2-amino-1-acenaphthenyl (*S*)-2-phenylpropionate (II-23a)

Chemical Formula	$C_{26}H_{27}NO_4$
Formula Weight	417.00
Crystal Size	0.80 × 0.25 × 0.15
a/Å	16.337 (8)
b/Å	5.282 (3)
c/Å	13.008 (7)
β/degree	100.82 (4)
Volume of Unit Cell	1103 (1)
Crystal System	Monoclinic
Space Group	$P2_1$
Z value	2
D_{calc}/g cm^{-3}	1.26
Reflections used	2047
No. of Variables	361
R;Rw	0.051; 0.064
Goodness of Fit	2.44
Maximum Shift/e. s. d. in final cycle	1.54
Maximum Negative Peak in Final Diff. Map/e Å^{-3}	–0.31
Maximum Positive Peak in Final Diff. Map/e Å^{-3}	0.39

Positional parameters and equivalentisotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B (eq)
O 1	-0.2152 (1)	-0.06359 (7)	-0.2471 (2)	4.70 (6)
O 2	-0.2722 (2)	0.1061 (7)	-0.5753 (2)	4.54 (6)
O 3	-0.3210 (2)	0.4077 (7)	-0.4787 (2)	5.39 (8)
O 4	-0.1501 (2)	0.2795 (9)	-0.2856 (5)	10.1 (2)
N 5	-0.3231 (2)	-0.0074 (8)	-0.4366 (2)	4.49 (7)
C 6	0.0464 (2)	0.1220 (9)	-0.1952 (3)	4.34 (8)
C 7	-0.4106 (2)	-0.1781 (8)	-0.3158 (2)	3.73 (8)
C 8	-0.4364 (2)	-0.376 (1)	-0.1528 (3)	4.51 (8)
C 9	-0.3289 (2)	-0.0498 (9)	-0.1565 (2)	4.19 (8)
C 10	-0.4708 (2)	-0.326 (1)	-0.3732 (3)	4.60 (9)
C 11	-0.5132 (2)	-0.502 (1)	-0.3219 (3)	5.1 (1)
C 12	-0.3932 (2)	-0.2062 (9)	-0.2059 (2)	3.89 (7)
C 13	-0.0063 (2)	-0.0848 (8)	-0.1976 (3)	4.33 (8)
C 14	-0.1507 (2)	0.0585 (9)	-0.2700 (4)	5.4 (1)
C 15	-0.3570 (2)	0.0350 (9)	-0.3436 (3)	4.13 (8)
C 16	0.0106 (3)	-0.2596 (9)	-0.1177 (4)	5.6 (1)
C 17	-0.1777 (3)	0.462 (1)	-0.5854 (4)	6.3 (1)
C 18	-0.2905 (2)	0.0779 (9)	-0.2402 (3)	4.17 (8)
C 19	-0.0820 (2)	-0.119 (1)	-0.2858 (4)	5.5 (1)
C 20	-0.2426 (2)	0.2872 (9)	-0.6469 (3)	4.95 (9)
C 21	-0.3529 (3)	-0.209 (1)	0.0060 (3)	6.4 (1)
C 22	-0.3089 (2)	-0.049 (1)	-0.0501 (3)	5.7 (1)
C 23	-0.4972 (2)	-0.532 (1)	-0.2154 (3)	5.1 (1)
C 24	0.1150 (2)	0.149 (1)	-0.1155 (3)	4.9 (1)
C 25	-0.0614 (3)	-0.078 (2)	-0.3946 (4)	7.6 (2)
C 26	-0.4139 (2)	-0.372 (1)	-0.0420 (3)	5.9 (1)
C 27	0.0794 (3)	-0.231 (1)	-0.0379 (3)	6.4 (1)
C 28	-0.3150 (3)	0.434 (1)	-0.7080 (4)	7.3 (2)
C 29	-0.2015 (5)	0.114 (1)	-0.7154 (5)	9.0 (2)
C 30	0.1310 (3)	-0.027 (1)	-0.0368 (3)	5.6 (1)
C 31	-0.3060 (2)	0.1896 (90	-0.4955 (2)	3.94 (8)
H 6	0.042 (3)	0.25 (1)	-0.243 (3)	4.22 (0)
H 24	0.152 (3)	0.31 (1)	-0.108 (4)	4.83 (0)
H 30	0.173 (3)	-0.00 (1)	0.018 (4)	5.53 (0)
H 27	0.092 (3)	-0.36 (1)	0.020 (4)	6.19 (0)
H 16	-0.025 (3)	-0.39 (1)	-0.124 (4)	5.34 (0)
H 25A	-0.114 (4)	-0.10 (2)	-0.460 (4)	7.53 (0)
H 25B	-0.016 (4)	-0.19 (2)	-0.400 (5)	7.53 (0)

H 19	-0.099 (3)	-0.29 (1)	-0.281 (4)	5.32 (0)
H 18	-0.277 (3)	0.25 (1)	-0.222 (3)	4.04 (0)
H 22	-0.262 (3)	0.06 (1)	-0.016 (4)	5.63 (0)
H 21	-0.338 (3)	-0.22 (1)	0.087 (4)	6.36 (0)
H 26	-0.445 (3)	-0.46 (1)	-0.001 (4)	5.77 (0)
H 23	-0.527 (3)	-0.65 (1)	-0.176 (4)	4.97 (0)
H 11	-0.554 (3)	-0.60 (1)	-0.361 (4)	4.99 (0)
H 10	-0.480 (3)	-0.32 (1)	-0.447 (3)	4.51 (0)
H 15	-0.390 (3)	0.17 (1)	-0.346 (4)	3.99 (0)
H 5	-0.310 (3)	-0.17 (1)	-0.452 (4)	4.30 (0)
H 28A	-0.345 (4)	0.28 (2)	-0.744 (5)	7.26 (0)
H 28B	-0.341 (4)	0.53 (2)	-0.655 (5)	7.26 (0)
H 28C	-0.292 (4)	0.52 (2)	-0.764 (5)	7.26 (0)
H 29A	-0.255 (4)	0.06 (2)	-0.755 (5)	8.45 (0)
H 29B	-0.186 (4)	0.22 (2)	-0.766 (5)	8.45 (0)
H 29C	-0.144 (4)	0.00 (2)	-0.664 (5)	8.45 (0)
H 17A	-0.212 (4)	0.60 (1)	-0.551 (4)	6.11 (0)
H 17B	-0.154 (4)	0.59 (1)	-0.641 (4)	6.11 (0)
H 17C	-0.147 (4)	0.37 (1)	-0.590 (5)	6.11 (0)
H 25C	-0.042 (4)	0.07 (2)	-0.394 (6)	7.53 (0)

Intramolecular distances (Å) with e.s.d. in parentheses

atom atom	distance	atom atom	distance
O1 --C14	1.316 (5)	C9 --C12	1.395 (5)
O1 --C18	1.456 (4)	C9 --C18	1.514 (5)
O2 --C31	1.339 (4)	C10 --C11	1.399 (6)
O2 --C20	1.478 (5)	C11 --C23	1.369 (5)
O3 --C31	1.206 (6)	C13 --C16	1.379 (6)
O4 --C14	1.185 (6)	C13 --C19	1.532 (5)
N5 --C31	1.351 (6)	C14 --C19	1.506 (6)
N5 --C15	1.441 (5)	C15 --C18	1.578 (4)
C6 --C24	1.383 (4)	C16 --C27	1.387 (6)
C6 --C13	1.389 (6)	C17 --C20	1.517 (6)
C6 --C10	1.365 (5)	C19 --C25	1.530 (8)
C7 --C12	1.412 (4)	C20 --C28	1.510 (7)
C7 --C15	1.511 (6)	C20 --C29	1.520 (8)
C8 --C12	1.402 (6)	C21 --C26	1.374 (7)
C8 --C26	1.419 (5)	C21 --C22	1.402 (8)
C8 --C23	1.420 (6)	C24 --C30	1.373 (6)
C9 --C22	1.361 (5)	C27 --C30	1.366 (8)

Intramolecular angles (degrees) with e.s.d. in parentheses

atom atom atom	angle	atom atom atom	angle
C14 --O1 --C18	118.9 (3)	N5 --C15 --C18	115.2 (3)
C31 --O2 --C20	120.4 (4)	C7 --C15 --C18	103.9 (3)
C31 --N5 --C15	120.6 (4)	C13 --C16 --C27	120.7 (4)
C24 --C6 --C13	120.6 (4)	O1 --C18 --C9	106.5 (3)
C10 --C7 --C12	118.8 (4)	O1 --C18 --C15	109.2 (3)
C10 --C7 --C15	133.4 (3)	C9 --C18 --C15	103.7 (3)
C12 --C7 --C15	107.7 (3)	C14 --C19 --C25	109.7 (4)
C12 --C8 --C26	115.6 (4)	C14 --C19 --C13	110.0 (4)
C12 --C8 --C23	116.7 (3)	C25 --C19 --C13	112.9 (3)
C26 --C8 --C23	127.8 (4)	O2 --C20 --C28	110.4 (4)
C22 --C9 --C12	119.1 (4)	O2 --C20 --C17	110.0 (3)
C22 --C9 --C18	132.6 (4)	O2 --C20 --C29	102.3 (4)
C12 --C9 --C18	108.1 (3)	C28 --C20 --C17	111.4 (4)
C7 --C10 --C11	119.3 (3)	C28 --C20 --C29	113.0 (4)
C23 --C11 --C10	122.7 (4)	C17 --C20 --C29	109.5 (4)
C9 --C12 --C8	123.9 (3)	C26 --C21 --C22	122.8 (4)
C9 --C12 --C7	113.3 (3)	C9 --C22 --C21	118.6 (4)
C8 --C12 --C7	122.8 (3)	C11 --C23 --C8	119.7 (4)
C16 --C13 --C6	118.3 (3)	C30 --C24 --C6	120.2 (4)
C16 --C13 --C19	120.3 (4)	C21 --C26 --C8	119.9 (4)
C6 --C13 --C19	121.3 (4)	C30 --C27 --C16	120.3 (5)
O4 --C14 --O1	123.6 (4)	C27 --C30 --C24	119.8 (4)
O4 --C14 --C19	124.0 (4)	O3 --C31 --O2	125.6 (4)
O1 --C14 --C19	112.0 (4)	O3 --C31 --N5	124.2 (3)
N5 --C15 --C7	114.6 (3)	O2 --C31 --N5	110.1 (4)

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Section II. Application of *cis*-2-Amino-1-acenaphthenol as a Precursor of Chiral Templates

1. Introduction

Chiral oxazolidinones[1] and oxazolines[2] can be easily derived from chiral 1,2-amino alcohols and have been widely used as efficient chiral templates in asymmetric synthesis. In Chapter II, Section I, the author described the design, synthesis, and resolution of a novel artificial chiral amino alcohol, *cis*-2-amino-1-acenaphthenol (**II-7**). The author next tried to convert this new chiral amino alcohol into the corresponding chiral oxazolidinone and oxazoline, which would be versatile chiral templates in various kinds of diastereoselective reactions. This amino alcohol has several structural characteristics, which are favorable when converted into oxazolidinone and oxazoline: 1) The orientation of the naphthalene ring is fixed to protrude in a direction favorable for efficient shielding of one diastereoface of the corresponding enolate having oxazolidinone moiety. 2) Oxazoline-containing substrates derived from **II-7** are expected to be stable under various conditions because fixation of the orientation of the amino and hydroxyl groups would make the corresponding oxazoline ring stable and avoid its destructive ring opening reaction. In this section, the author describes the application of **II-7** as a precursor for new chiral oxazolidinone- and oxazoline-type chiral templates and their respective applications to the diastereoselective alkylation of the corresponding lithium imide enolate and the diastereoselective [2,3]-Wittig rearrangement.

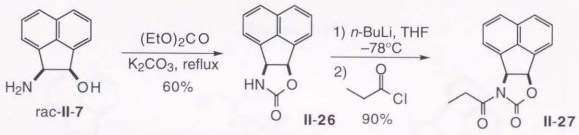
2. Results and Discussion

2.1 Diastereoselective Alkylation Reaction Using a Chiral Oxazolidinone as a Chiral Template

The *N*-propionyloxazolidinone **II-27** was easily synthesized form rac-**II-7** according to the standard procedure (Scheme II-15).[3] When the lithium enolate of **II-27** was allowed to react with allyl bromide,[4] the diastereoselectivity was >99:1 (Scheme II-16), which was superior to that observed when an oxazolidinone derived from *erythro*-2-amino-1,2-diphenylethanol (**II-1**) was used (d.r.=92:8). However, the yield of the desired allylated product **II-28** was quite low, and the parent oxazolidinone **II-26** was mainly recovered. Similar phenomenon was also observed in the reaction of the **II-1**-derived oxazolidinone,

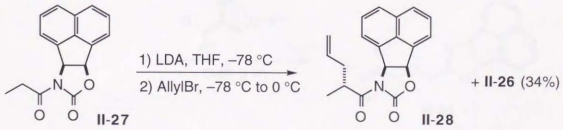
indicating that these lithium enolates **II-3** and **II-10**, derived from the corresponding 4,5-biaryloxazolidinones, easily decompose with releasing a ketene to give an anion of oxazolidinone **II-29**, which is supposed to be stabilized by the electron withdrawing effect of the aryl substituents at the 4- and 5-positions of the oxazolidinones. Thus, *N*-acyloxazolidinones, derived from amino alcohols having a benzylamine skeleton, were considered to be unfavorable for reactions via their lithium enolates. This problem was solved afterward by development of an amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol, which does not contain a "benzylamine" skeleton (described in Chapter III).

Scheme II-15



rac-**II-7** **II-26** 90% **II-27**

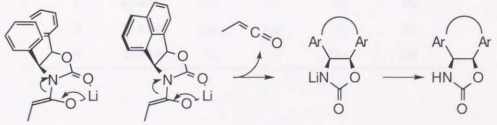
Scheme II-16



II-27 **II-28** + **II-26** (34%)

8%, d.r.>99:1

Scheme II-17



II-3 **II-10** **II-29**

2.2. The Diastereoselective [2,3]-Wittig Rearrangement Using a Chiral Oxazoline as a Chiral Template

Next, the author tried to apply **II-7** as a precursor of an oxazoline-type template for another reaction. The author chose the [2,3]-Wittig sigmatropic rearrangement,[5] since among several kinds of chiral templates reported so far a chiral oxazoline protocol is known to be very efficient.[6] Following this consideration, 2-chloromethyloxazoline **II-30** was synthesized from rac-**II-7** and imino ether hydrochloride and allowed to react with potassium salts of the required allylic alcohols in order to prepare substrates for the rearrangement, 2-(allyloxy)methyloxazolines **II-31** (Scheme II-18, Table II-2), which were quite stable in contrast to the corresponding oxazolines derived from *erythro*-2-amino-1,2-diphenylethanol.

Scheme II-18

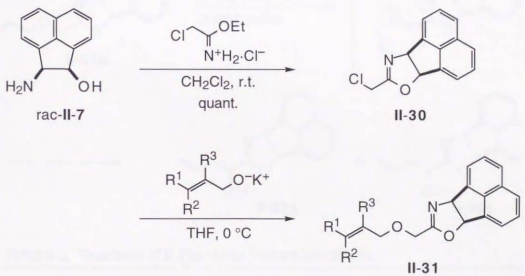
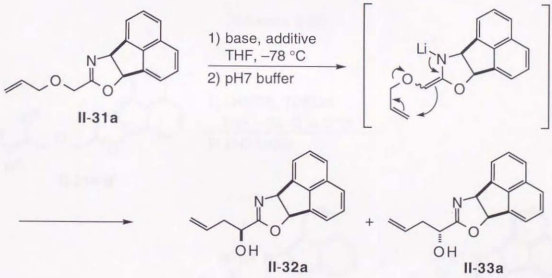


Table II-2. Yields of **II-31**

entry	**II-31**	R^1	R^2	R^3	yield/%
1	**II-31a**	H	H	H	81
2	**II-31b**	Me	H	H	86
3	**II-31c**	Me	Me	H	65
4	**II-31d**	H	H	Me	84

At first, the rearrangement was performed by using butyllithium as a base (Scheme II-19, Table II-3, entry 1). The reaction proceeded at –78 °C to give a diasteromeric mixture of the products (**II-32a**:**II-33a**=73:27), which were enough stable under silica gel chromatography. In the course of this study, other solvents, such as ether, hexane, and dimethoxyethane, were also used, but only depression of the selectivity was observed. In order to elucidate the effect of the counter cation of the azaenolate, **II-31a** was treated with butyllithium in THF at -78 °C in the presence of various kinds of metal halides (KBr, $MgCl_2$, Cp_2TiCl_2, Cp_2ZrCl_2, $ZnBr_2$, $SnCl_4$, $CuCl_2$).[7] However, the diastereoselectivity was not affected by the counter cation and, therefore, Li was used. The results are summarized in Table II-3.

Scheme II-19



II-31a **II-32a** **II-33a**

Table II-3. Reactions of **II-31a** Under Various Conditions

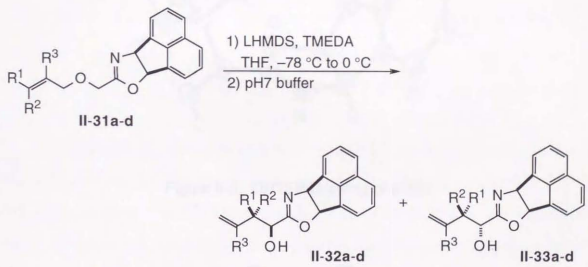
entry	base	additive	yield/%	**II-32a**:**II-33a**[a]
1	*n*-BuLi	–	58	73:27
2	*t*-BuLi	–	44	66:34
3	LDA	–	52	79:21
4	LDA	HMPA	35	77:23
5	LDA	TMEDA	64	76:24
6[b]	LHMDS	–	10	80:20
7[b]	LHMDS	TMEDA	55	79:21

[a] Determined by 400 MHz ^{1}H-NMR. [b] The reaction temperature was allowed to raise from –78 to 0 °C.

Among the bases examined, the highest selectivity was achieved when lithium hexamethyldisilazide (LHMDS) was used (Table II-3, entry 6). Because of the relatively low basicity of LHMDS, the reaction did not proceed at –78 °C, and the reaction temperature was allowed to raise from –78 °C to 0 °C. Moreover, the addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) remarkably improved the chemical yield without serious depression of the diastereoselectivity (entries 5 vs 3 and entries 7 vs 6). In contrast, the addition of hexamethylphosphoric triamide (HMPA) resulted in the decrease of the chemical yield (entries 4 vs 3).

Under the optimized reaction conditions, the reaction of **II-31** was carried out (Scheme II-20), and the results are summarized in Table II-4.

Scheme II-20



II-31a-d → **II-32a-d** + **II-33a-d**

Table II-4. Reactions of Allyl Ether Substrates **II-31**

Entry	**II-31**	R^1	R^2	R^3	Yield / %	**II-32**:**II-33**
1	**II-31a**	H	H	H	55	79:21
2	**II-31b**	Me	H	H	73	75(98:2[a]):25(96:4[a])
3	**II-31c**	Me	Me	H	75	59[b]:41
4	**II-31d**	H	H	Me	62	82:18

[a] *Syn*:*anti*. [b] The relative configuration was determined by X-ray crystallography.

The relative stereochemistry of major product **II-32c** (entry 3) was determined by a X-ray crystallographic analysis (Fig. II-3). The relative stereochemistries of the other major products were correlated with that of **II-32c** by the ^{1}H-NMR spectral data. In all cases, the chemical shift of the α-proton of the oxazoline in the major product was higher than that of the minor product. This difference in chemical shift can be explained as follows: The hydrogen bonding between the hydroxyl group and the nitrogen atom in the oxazoline ring is assumed to fix the conformation. Therefore, Hα of the major product is more shielded by the naphthalene ring than that of the minor product (Fig. II-4).[8]

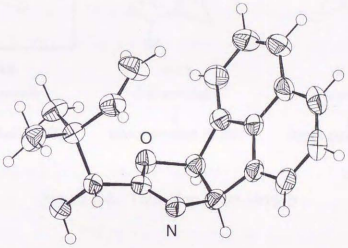


Figure II-3. ORTEP Drawing of II-32c

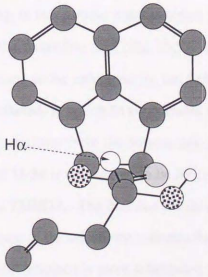
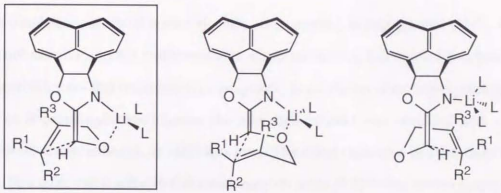


Figure II-4. Most Stable Conformation of II-32a[8]

In the reaction of **II-31b** (entry 2), four diastereomers were obtained, and the relative stereochemistry of major isomers of **II-32b** and **II-33b** was determined to be *syn* by the comparison of their ^{1}H-NMR data with those of the rearrangement products obtained from achiral 2-(2-propenyloxy)methyloxazolines.[9]



II-34
E-azaenolate
↓
major product (**II-32**)

II-35
E-azaenolate
↓
minor product (**II-33**)

II-36
Z-azaenolate
↓
minor product (**II-33**)

Figure II-5. Transition State Models

Several characteristics are evident from these data. 1) Unexpectedly, the introduction of R^1 and R^2 decreases the diastereoselectivity. 2) In the case of entry 2, *syn* selectivity is very high. 3) The introduction of R^3 increases the selectivity. These tendencies are explained by a transition state model, which is almost the same as that proposed by Nakai and his co-workers;[5,6] the oxazoline ring in the pseudo-axial position prevents the gauche repulsive interaction between R^1 and the oxazoline ring (Fig. II-5). The high *syn* selectivity of the crotyloxy derivative is explained to be enhanced by the bulkiness of the chiral auxiliary. Kinetically, model **II-34** is preferred, in which Li coordinates with the ether oxygen of the *E*-azaenolate, and the allyl group migrates from the bottom side of the enolate. When TMEDA was used as an additive, model **II-34** is considered to be more stabilized by a chelation of Li with the two nitrogen atoms of TMEDA. The fact that the introduction of alkyl groups to the allyl terminus leads to the decrease of the selectivity indicates the existence of *E-Z* isomerization of the azaenolate. When the allyl terminus is more substituted, the *Z*-enolate is supposed to be formed before the reaction proceeds. As shown in model **II-36**, the bottom-side rearrangement

of the *Z*-enolate gives the minor product. Another pathway to produce the minor product is shown in model **II-35**, although in this model R^3 is close to the naphthalene ring. When R^3 is Me, the repulsive interaction prevents the top-side rearrangement via **II-35** to increase the diastereofacial selectivity.

In conclusion, artificial amino alcohol, *cis*-2-amino-1-acenaphthenol (**II-7**), of which both enantiomeric forms are easily available via its resolution, was applied as a precursor of chiral oxazolidinone- and oxazoline-type templates. In alkylation of the corresponding lithium enolate of *N*-propionyloxazolidinone, the alkylated product was obtained with excellent diastereoselectivity, although its yield was low. The chiral oxazoline derived from **II-7** was found to be a quite stable and effective chiral template in the [2,3]-Wittig rearrangement.

3. Experimental

General information is same as that of Experimental in Chapter II, Section I.

(6b*R,9a*S**)-8-Chloromethyl-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (II-30)**. To a solution of rac-**II-7** (425 mg, 2.29 mmol) and ethyl 2-chloroacetimidate hydrochloride (362 mg, 2.29 mmol) in 30 mL of CH_2Cl_2 was added 0.5 mL of triethylamine at room temperature under Ar, and the reaction mixture was stirred at that temperature for 17 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 4:1) to give 561 mg (2.29 mmol, 100%) of **II-30** as a cream-white solid: Mp 132.0-133.0 °C; IR (KBr) 1660, 1340, 1268, 1162, 1033, 963, 940; ^{1}H-NMR (270 MHz; $CDCl_3$) 4.06 (1H, d, *J*=13), 4.16 (1H, d, *J*=13), 6.04 (1H, d, *J*=7.6), 6.36 (1H, d, *J*=7.3), 7.54-7.84 (6H, m); EI-MS 84 (44.2), 140 (39.0), 166 (100.0), 243 (M^+, 41.8); HR-MS calcd for $C_{14}H_{10}ClNO$ 243.0451, found 243.0434.

(6b*R,9a*S**)-8-(2-Propenyloxy)-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (II-31a)**. Under Ar, KH (53.1 mg, 1.32 mmol, mineral oil dispersion) was washed with hexane (2 mL × 3), and 1 ml of THF was added. To this suspension was added allyl alcohol (93.2 mg, 1.60 mmol) drop by drop over a period of 5 min at 0 °C. After the solution was stirred for 30 min at room temperature, **II-30** (269 mg, 1.10 mmol) in 2 mL of THF was

added drop by drop over a period of 10 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred for additional 30 min. The reaction was quenched by adding 10 mL of water. The solution was extracted with CH_2Cl_2 (10 mL × 3) and purified by column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 4:1) to give 235 mg (0.887 mmol, 81%) of **II-31a** as a pale yellow syrup: IR (neat) 1670, 1105, 972, 937, 835, 786; ^{1}H-NMR (400 MHz; $CDCl_3$) 4.01 (2H, m), 4.10 (2H, s), 5.14 (1H, dd, *J*=3.1, 10.4), 5.21 (1H, dd, *J*=3.1, 17.4), 5.85 (1H, m), 6.00 (1H, d, *J*=7.6), 6.28 (1H, d, *J*=7.3), 7.54-7.82 (6H, m); EI-MS 140 (30.7), 152 (100.0), 167 (71.0), 265 (M^+, 25.0); HR-MS calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1095.

(6b*R,9a*S**)-8-[(*E*)-2-Butenyloxy]-2*H*[6b,9a]-acenaphthyleno[1,2-*d*] oxazole (II-31b)**. A similar procedure described for the preparation of **II-31a** was applied and yielded **II-31b** (86%) as a pale yellow syrup by using 2-buten-1-ol (*E*:*Z*>99:1) as an alcohol. The *E*:*Z* ratio of **II-31b** was determined to be 98:2 by ^{1}H-NMR (400 MHz): IR (neat) 1665, 1110, 970, 932, 835, 785; ^{1}H-NMR (400 MHz; $CDCl_3$) 1.51 (3H×0.98, d, *J*=7.0), 1.63 (3H, dd, *J*=1.5, 6.2), 3.93 (2H, m), 4.08 (2H, s), 5.51 (1H, dt, *J*=7.0, 15.4), 5.65 (1H, dd, *J*=6.2, 15.4), 6.00 (1H, d, *J*=7.7), 6.29 (1H, d, *J*=7.7), 7.52-7.82 (6H, m); EI-MS 55 (40.5), 140 (21.7), 152 (100.0), 167 (78.6), 194 (16.9), 209 (16.9), 279 (M^+, 17.7); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1261.

(6b*R,9a*S**)-8-(3-Methyl-2-butenyloxy)-2*H*[6b,9a]-acenaphthyleno [1,2-*d*]oxazole (II-31c)**. A similar procedure described for the preparation of **II-31a** was applied and yielded **II-31c** (65%) as a pale yellow syrup by using 3-methyl-2-buten-1-ol as an alcohol: IR (neat) 1660, 1100, 965, 925, 832, 793; ^{1}H-NMR (270 MHz; $CDCl_3$) 1.53 (3H, s), 1.66 (3H, s), 3.98 (2H, d, *J*=7.3), 4.08 (2H, s), 5.28 (1H, t, *J*=7.3), 6.00 (1H, d, *J*=7.6), 6.28 (1H, d, *J*=7.6), 7.56-7.82 (6H, m); EI-MS 69 (25.5), 139 (18.5), 152 (92.2), 167 (100.0), 194 (16.2), 209 (32.7), 293 (M^+, 12.5); HR-MS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1428.

(6b*R,9a*S**)-8-(2-Methyl-2-propenyloxy)-2*H*[6b,9a]-acenaphthyleno [1,2-*d*]oxazole (II-31d)**. A similar procedure described for the preparation of **II-31a** was applied and yielded **II-31d** (84%) as a pale yellow syrup by using 2-methyl-2-propen-1-ol as an alcohol: IR (neat) 1660, 1100, 1018, 970, 905, 830, 792; ^{1}H-NMR (270 MHz; $CDCl_3$)

1.67 (3H, s), 3.92 (2H, dd, *J*=12.4, 16.8), 4.07 (2H, s), 4.84 (1H, d, *J*=2.0), 4.89 (1H, d, *J*=2.0), 6.01 (1H, d, *J*=7.3), 6.29 (1H, d, *J*=7.6), 7.50-7.83 (6H, m); EI-MS 55 (27.9), 139 (21.2), 152 (100.0), 194 (20.0), 194 (18.3), 279 (M^+, 15.6); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1239.

The General Procedure for the [2,3]-Wittig Rearrangement of II-31. The general procedure is exemplified for the reaction of **II-31c**. To a stirred solution of 118 mg (0.734 mmol) of TMS_2NH in THF (2 mL) at –78 °C was added *n*-BuLi (0.34 mL, 1.61 M in hexane, 0.54 mmol) drop by drop over a period of 1 min. After 30 min, a solution of TMEDA (94.4 mg, 0.812 mmol) in THF (1 mL) was added drop by drop over a period of 3 min at –78 °C, and the solution was stirred for 25 min. At –78 °C, a solution of **II-31c** (103 mg, 0.351 mmol) in THF (2 mL) was added to the reaction mixture drop by drop over a period of 10 min. Then, the reaction mixture was allowed to warm to 0 °C and stirred for 1.5 h. The reaction was quenched by adding 10 mL of pH 7 buffer. The solution was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by PTLC (hexane:AcOEt 2:1) to give 45.9 mg (45%) of **II-32c** (lower *Rf*) and 31.6 mg (31%) of **II-33c**.

(6b*R,9a*S**)-8-[(*R**)-1-Hydroxy-3-butenyl]-2*H*[6b,9a]-acenaphthyleno [1,2-*d*]oxazole (II-32a).** Obtained as a mixture with **II-33a** (**II-32a**:**II-33a**=79:21, determined by ^{1}H-NMR): Mp 179.7-182.5 °C; IR (KBr) 3400, 1660, 1180, 1100, 978, 922, 833, 782; ^{1}H-NMR (400 MHz; $CDCl_3$) 2.35 (2H × 0.21, m), 2.50 (2H × 0.79, m), 2.95 (1H × 0.21, br s), 3.00 (1H × 0.79, br s), 4.27 (1H × 0.79, pseudo q, *J*=7.1), 4.36 (1H × 0.21, pseudo q, *J*=7.1), 4.80 (2H × 0.21, m), 5.10 (2H × 0.79, m), 5.51 (1H × 0.21, m), 5.56 (1H × 0.79, m), 5.94 (1H × 0.21, d, *J*=7.2), 5.96 (1H × 0.79, d, *J*=7.2), 6.31 (1H × 0.21, d, *J*=7.2), 6.32 (1H × 0.79, d, *J*=7.2), 7.58-7.82 (6H, m); EI-MS 69 (11.7), 139 (20.7), 152 (100.0), 168 (40.0), 194 (17.8), 265 (M^+, 24.7); HR-MS calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1115.

(6b*R,9a*S**)-8-[(1*R**,2*S**)-1-Hydroxy-2-methyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (II-32b).** Obtained as a mixture of *syn*- and *anti*-isomers (*syn*:*anti*=98:2, determined by ^{1}H-NMR): White solid; mp 131.5-133.0 °C; IR (KBr) 3200, 1680, 1228, 1062, 977, 920, 832, 788; ^{1}H-NMR (400 MHz; $CDCl_3$) 1.03 (3H × 0.98, d,

J=7.0), 1.10 (3H × 0.02, d, *J*=7.0), 2.60 (1H, m), 2.76 (1H, br s), 4.08 (1H × 0.02, t, *J*=4.8), 4.17 (1H × 0.98, t, *J*=5.0), 4.94 (1H, d, *J*=12.3), 5.01 (1H, d, *J*=19.7), 5.77 (1H, m), 5.98 (1H, d, *J*=7.3), 6.34 (1H, d, *J*=7.3), 7.52-7.83 (6H, m); EI-MS 139 (15.3), 152 (100.0), 168 (36.6), 194 (14.0), 279 (M^+, 18.4); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1269.

(6b*R,9a*S**)-8-[(1*S**,2*R**)-1-Hydroxy-2-methyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (II-33b)**. Obtained as a mixture of *syn*- and *anti*-isomers (*syn*:*anti*=96:4, determined by ^{1}H-NMR). White solid; mp 157.8-159.2 °C; IR (KBr) 3175, 1677, 1040, 957, 8323, 780; ^{1}H-NMR (400 MHz; $CDCl_3$) 0.70 (3H × 0.96, d, *J*=6.7), 0.94 (3H × 0.04, d, *J*=7.0), 2.47 (1H, m), 2.72 (1H, d, *J*=5.2), 4.18 (1H × 0.04, t, *J*=5.1), 4.25 (1H × 0.96, t, *J*=5.3), 4.82 (1H, d, *J*=10.5), 4.88 (1H, d, *J*=19.3), 5.63 (1H, m), 5.95 (1H, d, *J*=7.3), 6.32 (1H, d, *J*=7.3), 7.52-7.83 (6H, m); EI-MS 139 (15.1), 152 (100.0), 168 (39.5), 194 (12.4), 279 (M^+, 14.8); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1250.

(6b*R,9a*S**)-8-[(*R**)-1-Hydroxy-2,2-dimethyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (II-32c)**. White solid; mp 131.8-132.0 °C; IR (KBr) 3200, 1643, 1078, 980, 838, 782; ^{1}H-NMR (400 MHz; $CDCl_3$) 0.99 (3H, s), 1.04 (3H, s), 2.82 (1H, d, *J*=6.3), 3.93 (1H, d, *J*=6.1), 4.97 (1H, d, *J*=14.3), 5.00 (1H, d, *J*=10.7), 5.83 (1H, dd, *J*=10.0, 14.4), 5.94 (1H, d, *J*=7.3), 6.28 (1H, d, *J*=7.3), 7.52-7.81 (6H, m); EI-MS 139 (10.5), 152 (100.0), 168 (34.2), 194 (12.7), 293 (M^+, 11.9); HR-MS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1428.

(6b*R,9a*S**)-8-[(*S**)-1-Hydroxy-2,2-dimethyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (II-33c)**. White solid; mp 132.0-132.3 °C; IR (KBr) 3150, 1643, 1068, 975, 830, 781; ^{1}H-NMR (400 MHz; $CDCl_3$) 0.85 (3H, s), 0.87 (3H, s), 2.80 (1H, br s), 3.98 (1H, s), 4.66 (1H, d, *J*=14.4), 4.75 (1H, d, *J*=9.8), 5.63 (1H, dd, *J*=9.8, 14.6), 5.94 (1H, d, *J*=7.3), 6.29 (1H, d, *J*=7.3), 7.50-7.81 (6H, m); EI-MS 139 (9.9), 152 (100.0), 168 (37.7), 194 (10.4), 293 (M^+, 11.7); HR-MS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1430.

(6b*R,9a*S**)-8-[(*R**)-1-Hydroxy-3-methyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (II-32d)**. Obtained as a mixture with **II-33d** (**II-**

32d:**II-33d**=82:18, determined by ^{1}H-NMR): Mp 115.0-119.0 °C; IR (KBr) 3280, 1660, 1105, 1065, 904, 814, 783; ^{1}H-NMR (400 MHz; $CDCl_3$) 1.58 (3H × 0.82, s), 1.72 (3H × 0.18, s), 2.31 (2H × 0.82, m), 2.40 (2H × 0.18, m), 2.62 (1H × 0.82, br s), 3.01 (1H × 0.18, br s), 4.35 (1H × 0.18, m), 4.43 (1H × 0.82, m), 4.64 (2H × 0.82, d, *J*=19.0), 4.80 (2H × 0.18, d, *J*=30.0), 5.93 (1H × 0.18, d, *J*=7.3), 5.98 (1H × 0.82, d, *J*=7.3), 6.32 (1H, d, *J*=7.3), 7.60-7.82 (6H, m); EI-MS 55 (13.8), 139 (17.9), 152 (100.0), 167 (67.5), 194 (15.5), 278 (33.9), 279 (M^+, 29.4); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1283.

Detailes for X-ray structural analysis of (6b*R,9a*S**)-8-[(*R**)-1-Hydroxy-2,2-dimethyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (II-32c).**

Chemical Formula	$C_{19}H_{19}NO_2$
Formula Weight	293.00
Crystal Size	0.40 × 0.20 × 0.20
a/Å	10.136 (1)
b/Å	26.755 (3)
c/Å	5.6996 (8)
Volume of Unit Cell	1545.6 (4)
Crystal System	Orthorhombic
Space Group	$P2_12_12_1$
Z value	4
D_{calc}/g cm^{-3}	1.26
Reflections used	1530
No. of Variables	257
R;Rw	0.045; 0.050
Goodness of Fit	1.93
Maximum Shift/e. s. d. in final cycle	0.38

Maximum Negative Peak in Final Diff. Map/e Å^{-3}	–0.36
Maximum Positive Peak in Final Diff. Map/e Å^{-3}	0.21

Positional parameters and equivalentisotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B (eq)
O 1	-0.3205 (2)	0.10307 (6)	-0.1755 (3)	3.22 (4)
O 2	-0.4681 (2)	0.00788 (7)	-0.1724 (4)	4.02 (5)
N 3	-0.1871 (2)	0.05515 (7)	0.0466 (4)	3.03 (5)
C 4	-0.3020 (2)	0.06412 (8)	-0.0277 (4)	2.68 (5)
C 5	-0.1029 (2)	0.17447 (9)	0.1196 (5)	3.08 (6)
C 6	-0.1924 (3)	0.17761 (9)	-0.0675 (5)	3.17 (6)
C 7	-0.0986 (2)	0.09392 (9)	-0.0519 (5)	3.17 (6)
C 8	-0.0420 (2)	0.12736 (9)	0.1368 (5)	3.08 (6)
C 9	-0.0775 (3)	0.21388 (9)	0.2750 (5)	3.60 (7)
C 10	-0.2356 (3)	0.2617 (1)	0.0499 (8)	4.98 (9)
C 11	-0.5376 (2)	0.06333 (9)	0.1375 (4)	3.05 (5)
C 12	-0.1933 (2)	0.12823 (9)	-0.1943 (5)	3.12 (6)
C 13	-0.4801 (3)	0.0966 (1)	0.3242 (5)	3.78 (7)
C 14	-0.4216 (2)	0.03283 (9)	0.0299 (5)	2.85 (5)
C 15	-0.2591 (3)	0.2213 (1)	-0.1047 (6)	4.20 (8)
C 16	-0.1493 (3)	0.2588 (1)	0.2329 (7)	4.59 (8)
C 17	-0.6303 (3)	0.0251 (1)	0.2558 (6)	4.36 (8)
C 18	0.0785 (3)	0.1593 (1)	0.4662 (6)	4.42 (8)
C 19	0.0176 (3)	0.2047 (1)	0.4528 (6)	4.34 (7)
C 20	-0.6140 (3)	0.0919 (1)	-0.0501 (6)	3.87 (7)
C 21	0.0493 (2)	0.1194 (1)	0.3090 (6)	3.94 (7)
C 22	-0.4772 (4)	0.1454 (1)	0.3283 (6)	5.5 (1)
H 15	-0.313 (4)	0.223 (1)	-0.236 (8)	4.20 (0)
H 10	-0.289 (4)	0.293 (1)	0.029 (8)	4.98 (0)
H 16	-0.129 (4)	0.288 (1)	0.327 (8)	4.59 (0)
H 19	0.037 (4)	0.232 (1)	0.574 (7)	4.33 (0)
H 18	0.145 (4)	0.150 (1)	0.592 (8)	4.42 (0)
H 21	0.085 (3)	0.086 (1)	0.334 (8)	3.94 (0)
H 7	-0.029 (3)	0.077 (1)	-0.162 (7)	3.16 (0)
H 12	-0.172 (3)	0.131 (1)	-0.374 (7)	3.12 (0)
H 14	-0.388 (3)	0.008 (1)	0.147 (7)	2.85 (0)

H 2	-0.403 (4)	-0.010 (1)	-0.242 (8)	4.01 (0)
H 17A	-0.707 (4)	0.043 (1)	0.320 (8)	4.36 (0)
H 17B	-0.662 (4)	-0.001 (1)	0.130 (8)	4.36 (0)
H 17C	-0.583 (4)	0.008 (1)	0.387 (8)	4.36 (0)
H 20A	-0.560 (4)	0.116 (1)	-0.138 (7)	3.87 (0)
H 20B	-0.690 (4)	0.108 (1)	0.021 (7)	3.87 (0)
H 20C	-0.646 (4)	0.066 (1)	-0.170 (7)	3.87 (0)
H 13	-0.438 (4)	0.079 (1)	0.453 (7)	3.78 (0)
H 22A	-0.435 (4)	0.164 (1)	0.480 (9)	5.51 (0)
H 22b	-0.513 (4)	0.166 (2)	0.188 (9)	5.51 (0)

Intramolecular distances (Å) with e.s.d. in parentheses

atom atom	distance	atom atom	distance
O1 --C4	1.353 (3)	C8 --C21	1.365 (4)
O1 --C12	1.458 (3)	C9 --C19	1.420 (4)
O2 --C14	1.414 (3)	C9 --C16	1.425 (4)
N3 --C4	1.262 (3)	C10 --C16	1.353 (5)
N3 --C7	1.482 (3)	C10 --C15	1.414 (4)
C4 --C14	1.509 (3)	C11 --C3	1.505 (4)
C5 --C9	1.401 (4)	C11 --C20	1.526 (4)
C5 --C6	1.402 (4)	C11 --C17	1.544 (4)
C5 --C8	1.407 (3)	C11 --C14	1.557 (3)
C6 --C15	1.368 (4)	C13 --C22	1.307 (4)
C6 --C12	1.506 (4)	C18 --C19	1.363 (4)
C7 --C8	1.512 (4)	C18 --C21	1.425 (5)
C7 --C12	1.556 (4)		

Intramolecular angles (degrees) with e.s.d. in parentheses

atom atom atom	angle	atom atom atom	angle
C4 --O1 --C12	106.2 (2)	C16 --C10 --C15	122.7 (3)
C4 --N3 --C7	107.4 (2)	C13 --C11 --C20	113.3 (2)
N3 --C4 --O1	118.9 (2)	C13 --C11 --C17	108.6 (2)
N3 --C4 --C14	124.2 (2)	C13 --C11 --C14	107.2 (2)
O1 --C4 --C14	116.8 (2)	C20 --C11 --C17	109.3 (2)
C9 --C5 --C6	123.7 (2)	C20 --C11 --C14	111.7 (2)
C9 --C5 --C8	123.3 (2)	C17 --C11 --C14	106.5 (2)
C6 --C5 --C8	113.0 (2)	O1 --C12 --C6	112.0 (2)
C15 --C6 --C5	119.3 (2)	O1 --C12 --C7	103.6 (2)
C15 --C6 --C12	132.3 (3)	C6 --C12 --C7	105.3 (2)

C5 --C6 --C12	108.4 (2)	C22 --C13 --C11	127.8 (3)
N3 --C7 --C8	112.0 (2)	O2 --C14 --C4	110.6 (2)
N3 --C7 --C12	103.7 (2)	O2 --C14 --C11	108.5 (2)
C8 --C7 --C12	104.8 (2)	C4 --C14 --C11	113.7 (2)
C21 --C8 --C5	119.2 (2)	C6 --C15 --C10	118.3 (3)
C21 --C8 --C7	132.6 (2)	C10 --C16 --C9	120.3 (3)
C5 --C8 --C7	108.3 (2)	C19 --C18 --C21	122.5 (3)
C5 --C9 --C19	116.4 (2)	C18 --C19 --C9	120.1 (3)
C5 --C9 --C16	115.8 (3)	C8 --C21 --C18	118.4 (3)
C19 --C9 --C16	127.8 (3)		

4. References and Notes

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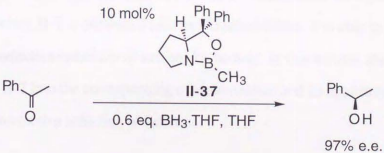
Section III. Application of *cis*-2-Amino-1-acenaphthenol as a Precursor of Chiral Catalysts

1. Introduction

Utilization of a chiral oxazaborolidine as a chiral reagent in enantioselective reduction of prochiral ketone was originally developed by Itsuno and his co-workers.[1] Further investigation concerning the improvement of this system by Corey and his co-workers revealed that a catalytic amount of oxazaborolidine is able to provide alcohols having predictable absolute configuration with high enantioselectivity and that among the oxazaborolidines examined *L*-proline-derived **II-37** is most effective (Scheme II-21).[2,3]

Scheme II-21



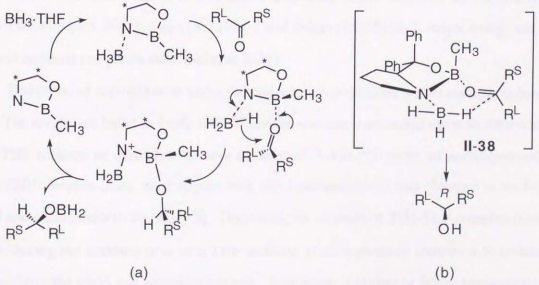


Figure II-6. Reaction Mechanism of Enantioselective Reduction of Ketone

The absolute configuration of the product and its excellent enantiopurity are explained by the transition state model **II-38**, which includes a rigid fused 5-5-6 membered ring (Fig. II-6(b)): The geometry of substituents (R^L: larger group, R^S: smaller group) of a ketone is considered to be determined so as to avoid the steric repulsion of the methyl group on the boron atom with R^L.

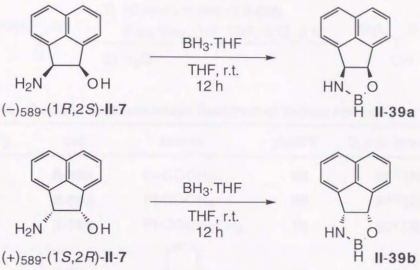
Oxazaborolidines are easily obtained from various 1,2-amino alcohols by treatment with various boron compounds and are enough stable to be stored.[2] Recently, it is reported that an oxazaborolidine, prepared *in situ* by mixing 1,2-amino alcohol with borane·dimethylsulfide complex, can be used in the enantioselective reduction of prochiral ketones and results in high enantioselectivity.[4] *cis*-2-Amino-1-acenaphthenol (**II-7**), of which the synthesis and resolution was described in Chapter II, Section I, has a structural characteristic that the orientation of the amino and hydroxyl groups are fixed due to the fused ring system of acenaphthene. Therefore, the author considered that this structural feature would be suitable for the construction of a rigid transition state; when **II-7** is converted into an oxazaborolidine, it is able to be applied to the catalytic enantioselective reduction of ketones by borane. In this section, the author describes the derivation of **II-7** into the corresponding oxazaborolidine and its application as a new chiral catalyst to enantioselective reduction of ketones.

2. Results and Discussion

Chiral oxazaborolidines **II-39a** and **II-39b** were easily prepared by the reaction of BH_3·THF complex with $(-)_{589}$-(1*R*,2*S*)-**II-7** and $(+)_{589}$-(1*S*,2*R*)-**II-7**, respectively, and used without isolation nor purification (Scheme II-22).

Reduction of acetophenone under various reaction conditions was examined (Scheme II-23). The results are listed in Table II-5. When the reaction was carried out with slow addition of a THF solution of acetophenone to a mixture of **II-39a** (10 mol% of acetophenone) and BH_3·THF complex (2 eq. of acetophenone), (*R*)-1-phenylethanol was obtained in the highest yield and enantioselectivity (entry 3). Decreasing the amount of BH_3·THF complex (entry 1) and reducing the addition time of a THF solution of acetophenone (entries 4,5) resulted in diminishing the yield and enantioselectivity. Moreover, a higher or lower temperature also resulted in lower yield and selectivity (entries 2,6).

Scheme II-22



(−)589-(1*R*,2*S*)-**II-7** **II-39a**

(+)589-(1*S*,2*R*)-**II-7** **II-39b**

Scheme II-23

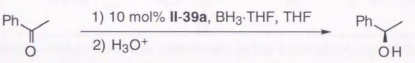


Table II-5. Catalytic Enantioselective Reduction of Acetophenone

entry	equiv. of BH_3·THF	temp./°C	addition time/min.	yield / %	% e.e.[a]
1	1.0	r.t.	120	69	89
2	2.0	r.t.	120	71	94
3	2.0	0	120	89	95
4	2.0	0	30	90	59
5	2.0	0	10	88	32
6	2.0	–20	120	73	56

[a] Determined by chiral HPLC analysis (Daicel Chiralcel OJ) .

Under the optimized conditions, used in entry 3 in Table II-5, reduction of several kinds of prochiral ketones was carried out to give the corresponding alcohols in good to excellent selectivity (Scheme II-24, Table II-6). It is noteworthy that both enantiomers of this artificial amino alcohol are readily available and that consequently both enantiomers of the desired alcohols should be equally easy to obtain (entries 1 and 2).

Scheme II-24

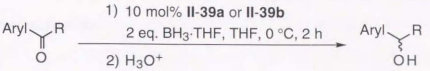


Table II-6. Catalytic Enantioselective Reduction of Various Ketones

entry	cat.	ketone	yield/%	% e.e. (config.)[a]
1	**II-39a**	$PhCOCH_3$	89	95[b] (*R*)
2	**II-39b**	$PhCOCH_3$	65	94[b] (*S*)
3	**II-39b**	$PhCOCH_2CH_3$	70	80[c] (*S*)
4	**II-39a**		87	92[c] (*R*)
5	**II-39a**		81	91[c] (*R*)

[a] The absolute configuration was determined on the basis of the sign of the specific rotation. [b] Determined by chiral HPLC analysis (Daicel Chiralcel OJ). [c] Determined by 270 MHz ^{1}H–NMR analysis of the corresponding MTPA ester of the product .

The absolute configurations of the products were in good agreement with the expectation based on a proposed transition state model **II-42** in Fig. II-7. Quallich and his co-workers performed detailed calculation concerning the transition state models for the enantioselective borane reduction catalyzed by a chiral oxazaborolidine of *erythro*-2-amino-1,2-diphenylethanol.[5] They concluded that among the possible geometries of the 5-6 fused ring system, *endo*-geometry **II-40** is more stable than *exo*-geometry **II-41**. On the basis of their results, the author excluded the transition state of similar *exo*-geometry. Among two models for *endo*-geometry, **II-42** is more favorable than **II-43** because steric repulsion between the larger substituent of ketone (R^L) and the hydrogen atoms on the boron atoms is avoided in **II-42**, whereas is serious in **II-43**. Thus, *R*-predominance of the product by using the oxazaborolidine, derived from (1*R*,2*S*)-**II-7**, can be explained. Moreover, since rigidity of the 5-5-6 fused ring system is reinforced by the rigid structure originated from the amino alcohol,

aforesaid steric repulsion in **II-43** is considered to be made more serious. Therefore, the reaction via transition state **II-42** is considered to be more preferable and consequently results in excellent enantioselectivity.

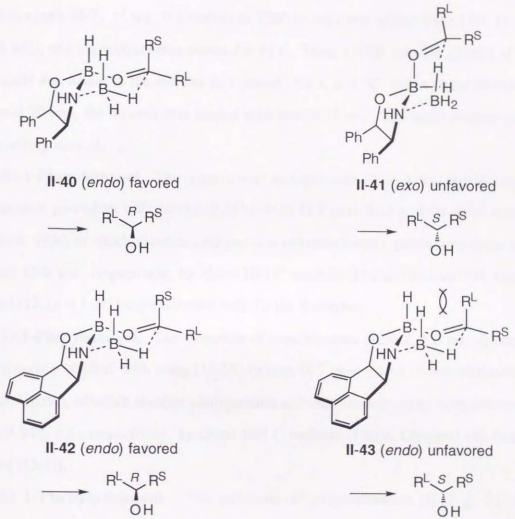


Figure II-7. Transition State Models

In conclusion, an artificial chiral amino alcohol, *cis*-2-amino-1-acenaphthenol, of which both enantiomeric forms are easily available via resolution, was converted into the corresponding chiral oxazaborolidine and applied to the catalytic enantioselective reduction of ketones. The reduction of various ketones with the chiral oxazaborolidine catalyst gave the corresponding enantioenriched alcohols in good to excellent enantioselectivities. With properly using both enantiomers of the oxazaborolidine, both enantiomers of the product alcohol were enantioselectively synthesized.

3. Experimental

General information is same as that of Experimental in Chapter II, Section I.

General Procedure for the Enantioselective Reduction of Ketone.

To a suspension of homochiral *cis*-2-amino-1-acenaphthenol ((1*R*,2*S*)-(–)589- or (1*S*,2*R*)-(+)589-**II-7**, 37 mg, 0.2 mmol) in THF (4 mL) was added BH_3·THF (1.0 M in THF, 4 mL), and the mixture was stirred for 12 h. Then, a THF solution (2 mL) of ketone (2.0 mmol) was added to the mixture in a period of 2 h at 0 °C. After being stirred for an additional 20 min, the mixture was treated with MeOH (5 ml). The usual workup gave the corresponding alcohol.

(*R*)-1-Phenylethanol. The reduction of acetophenone (0.24 g, 2.0 mmol) according to the general procedure with using (1*R*,2*S*)-(–)589-**II-7** gave 0.22 g of the titled compound (1.8 mmol, 89%), of which absolute configuration and enantiomeric purity were determined to be *R* and 95% e.e., respectively, by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/2-propanol (15:1), α 1.28, longer retention time for the *R* isomer).

(*S*)-1-Phenylethanol. The reduction of acetophenone (0.24 g, 2.0 mmol) according to the general procedure with using (1*S*,2*R*)-(+)589-**II-7** gave 0.16 g of the titled compound (1.3 mmol, 65%), of which absolute configuration and enantiomeric purity were determined to be *S* and 94% e.e., respectively, by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/2-propanol (15:1)).

(*S*)-1-Phenylpropanol. The reduction of propiophenone (0.27 g, 2.0 mmol) according to the general procedure with using (1*S*,2*R*)-(+)589-**II-7** gave 0.19 g of the titled compound (1.4 mmol, 70%) of which enantiomeric purity was determined to be 80% e.e. by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/2-propanol (15:1)): $[\alpha]^{21.0}_{589}$ –36.3 (c 1.50, $CHCl_3$) (lit. $[\alpha]^{20.0}_{589}$ –27.7 (neat)).[6]

(*R*)-1-(1-Naphthyl)ethanol. The reduction of 1-acetonaphthone (0.34 g, 2.0 mmol) according to the general procedure with using (1*R*,2*S*)-(–)589-**II-7** gave 0.30 g of the titled compound (1.7 mmol, 87%): $[\alpha]^{21.0}_{589}$ +59.7 (c 1.68, EtOH) (lit. [α]589 +74.4 (EtOH)).[7] The enantiomeric purity of the titled compound obtained here was determined to be 92% e.e. by 270 MHz ^{1}H-NMR analysis of the corresponding (+)-MTPA ester.

(*R*)-1,2,3,4-Tetrahydro-1-naphthol. The reduction of α-tetralone (0.29 g, 2.0 mmol) according to the general procedure with using (1*R*,2*S*)-(−)$_{589}$-**II-7** gave 0.24 g of the titled compound (1.6 mmol, 81%): $[\alpha]^{21.0}_{589}$ −27.9 (c 2.03, $CHCl_3$) (lit. $[\alpha]^{17.0}_{589}$ +32.7 (c 10.7, $CHCl_3$) for (*S*)-enantiomer).[8] The enantiomeric purity of the titled compound obtained here was determined to be 91% e.e. by 270 MHz ^{1}H-NMR analysis of the corresponding (+)-MTPA ester.

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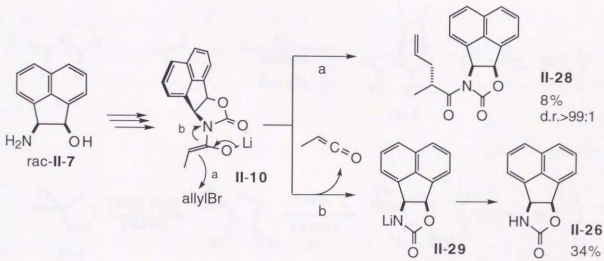
CHAPTER III. DEVELOPMENT AND APPLICATION OF *CIS*-2-AMINO-3,3-DIMETHYL-1-INDANOL

Section I. Design, Synthesis, and Resolution of *cis*-2-Amino-3,3-dimethyl-1-indanol

1. Introduction

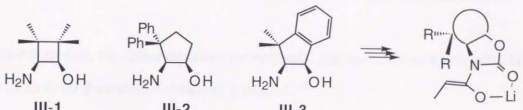
In the course of study concerning the development of highly useful artificial chiral auxiliaries, *cis*-2-amino-1-acenaphthenol (**II-7**) was developed and used as an useful precursor of a chiral oxazoline as mentioned in Chapter II. However, in diastereoselective alkylation of the lithium enolate of the *N*-propionyloxazolidinone derived from **II-7**, the enolate **II-10** easily decomposed to give deacylated oxazolidinone **II-26**, and the yield of the desired allylated product **II-28** was quite low (Scheme III-1).

Scheme III-1



The author considered that the low stability of the lithium enolate **II-10** arose from the facile release of a ketene to give an anion of oxazolidinone **II-29**, which is supposed to be stabilized by the electron withdrawing effect of the naphthyl ring of the oxazolidinone. Moreover, amino alcohol **II-7** itself was found to be somewhat unstable to air. This low stability of **II-7** seems to arise from its distorted naphthylamine structure. In order to solve

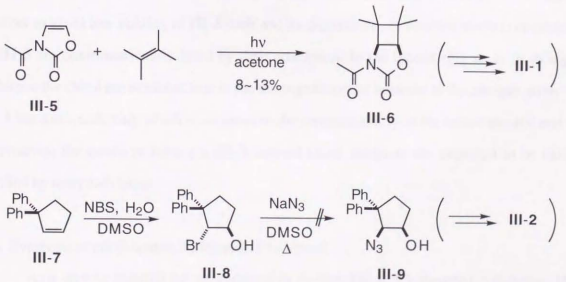
these problems, the author continued to seek new auxiliaries, which do not contain a "benzylamine" skelton and designed several new amino alcohols (Fig. III-1). These amino alcohols are not benzylamine-type compounds so that their better stability under various conditions was expected. Furthermore, these amino alcohols possess conformationally fixed bulky substituents, which would be effective in constructing chiral environment; for example, these two substituents attached to the 4- or 5-membered ring would effectively shield one side of the diastereoface of the corresponding enolates.



III-1 III-2 III-3 III-4

Figure III-1. Design of New Conformationally Rigid Artificial Amino Alcohols

Scheme III-2



First, the author investigated the synthesis of **III-1** via its corresponding *N*-acetyloxazolidinone ring was expected to be readily constructed by photo-induced [2+2] cycloaddition of **III-5** and 2,3-dimethyl-2-butene (Scheme III-2). However, when the cycloaddition was performed with irradiation of UV in acetone, the desired **III-6** was obtained

only in low yield.[1] Next, the author tried to synthesize **III-2** via *trans*-bromohydrin **III-8**, which is able to be easily obtained from 3,3-diphenyl-1-cyclopentene **III-7**.[2] However, azidation of **III-8** with sodium azide did not proceed, presumably because of bulkyness of the phenyl substituents of **III-8**. Therefore, the author designed *cis*-2-amino-3,3-dimethyl-1-indanol (**III-3**). Although the synthesis of racemic 2-amino-3,3-dimethyl-1-indanol has already been reported,[3] the stereochemistry of the product (*cis* or *trans*) and the reaction selectivity are unknown. Moreover, optically active **III-3** has not yet been reported. Thus the author focused his attention to develop the efficient method of synthesis and resolution of **III-3**.

In this section, the author describes the synthesis, and resolution of a new artificial chiral amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol.

2. Results and Discussion

2.1. Design of *cis*-2-Amino-3,3-dimethyl-1-indanol

cis-2-Amino-3,3-dimethyl-1-indanol **III-3** was designed so as to have following characteristics favorable as a chiral auxiliary: 1) **III-3** does not contain a "benzylamine" skelton in order to avoid low stability of **III-3** itself and its derivatives. 2) The two methyl substituents of **III-3** are conformationally fixed by their attachment to the indane ring so as to strongly influence the chiral environment near to the stereogenic center adjacent to the nitrogen atom. 3) **III-3** has a aromatic ring which contributes to the crystallizability of the amino alcohol and its derivatives; the products having a **III-3**-derived chiral template are expected to be easily purified by recrystallization.

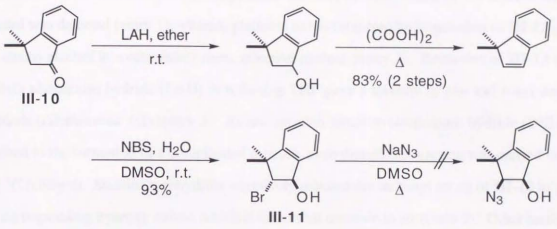
2.2. Synthesis of *cis*-2-Amino-3,3-dimethyl-1-indanol

As a starting material for the synthesis of racemic **III-3**, 3,3-dimethyl-1-indanone **III-10** was chosen. **III-10** was easily synthesized by the Friedel-Crafts reaction of 3-methyl-2-butenoic acid with benzene in a large quantity by following the procedure in the literature.[4]

First, the procedure via *trans*-bromohydrin, which was successfully applied to the preparation of racemic *cis*-2-amino-1-acenaphthenol (described in Chapter II), was attempted.

However, nucleophilic substitution of the bromohydrin **III-11** with azide anion did not proceeded (Scheme III-3).

Scheme III-3



Scheme III-4

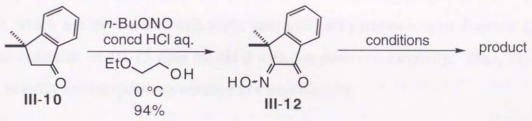


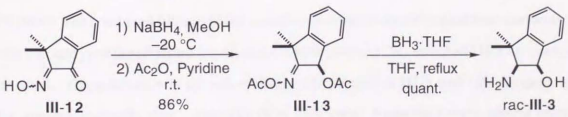
Table III-1. Reduction of **III-12** under Various Conditions

entry	conditions	products, yield/%, etc.
1	Pd-C, H_2, EtOH, HCl aq., r.t.	complex mixtures
2	PtO_2, H_2, MeOH, r.t.	amino alcohol, 76%, *trans*
3	LAH, THF, reflux	amino alcohol, *cis*:*trans*=1:1.5
4	DIBAL, CH_2Cl_2, –78 to 0 °C	complex mixtures
5	$NaBH_4$, MeOH, –20 °C	hydroxy oxime, 80~95% (crude)
6	$NaBH_4$, $ZrCl_4$, ether, r.t.	complex mixtures
7	reduction of acetate of oxime by BH_3·THF, THF, reflux	amino alcohol, *cis*:*trans*=1:1

Next, several attempts were made to obtain the desired rac-**III-3** by the reduction of oxime **III-12**, which was readily obtained by treatment of **III-10** with butyl nitrite under acidic conditions (Scheme III-4, Table III-1)).[5] Palladium/charcoal-catalyzed hydrogenation of **III-12** resulted in the formation of a complicated mixture, in which none of the desired amino alcohol was detected (entry 1), whereas platinum oxide-catalyzed hydrogenation of **III-12** gave the amino alcohol in a completely *trans* selective manner (entry 2). Reduction of **III-12** with lithium aluminium hydride (LAH) in refluxing THF gave a mixture of *cis*- and *trans*-amino alcohols (*cis*:*trans*=ca 1:2) (entry 3). Reduction with diisobutylaluminium hydride (DIBAL) resulted in the formation of a complicated mixture, even though the reaction was carried out at –78 °C (entry 4). Sodium borohydride selectively reduced the carbonyl group of **III-12** to give the corresponding hydroxy oxime, which is somewhat unstable to air (entry 5). Other methods examined in order to reduce the keto and imino groups at once were resulted in failure (entries 6 and 7).

Then, the author tried a stepwise route combining separate reductions of the keto and imino groups (Scheme III-5). Reduction of **III-12** with $NaBH_4$ in methanol gave the hydroxy oxime, which was then treated with acetic anhydride and pyridine to give diacetate **III-13**. Borane-reduction of **III-13** gave rac-**III-3** with complete *cis*-selectivity. Thus, rac-**III-3** could be easily and inexpensively obtained in a large quantity.

Scheme III-5

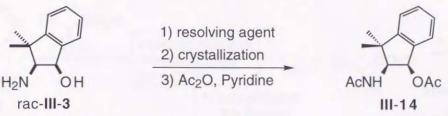


2.3. Resolution of *cis*-2-Amino-3,3-dimethyl-1-indanol

The resolution of rac-**III-3** was examined via crystallization of diastereomeric salts with chiral acids, such as camphorsulfonic acid, tartaric acid, and mandelic acid (Scheme III-6, Table III-2). Of these, mandelic acid was found to be very effective; upon crystallization of the salt of rac-**III-3** with (*S*)-mandelic acid from ethanol, (–)589-(1*R*,2*S*)-**III-3** was obtained in

40% yield with 96% e.e. as determined by chiral HPLC analysis (Daicel Chiralcel OD) of the *N*,*O*-diacetylated product **III-14**, which was obtained by treatment of **III-3** with acetic anhydride and pyridine.

Scheme III-6



rac-**III-3** **III-14**

Table III-2. Efficiency of Several Resolving Agents in Resolution of **III-3**

resolving agent	crystallization solvent	results[a]
mandelic acid	EtOH	40%, 96% e.e.
tartaric acid	EtOH/H_2O (3/1)	53%, 22% e.e.
camphorsulfonic acid	H_2O	not crystallized

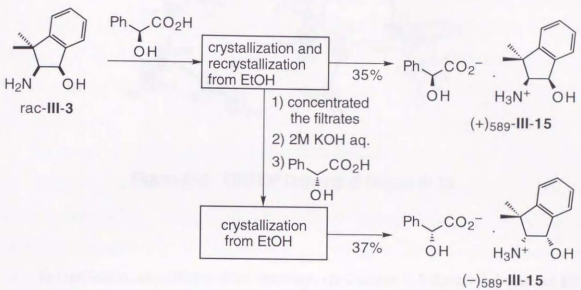
[a] The e.e. of **III-3** was determined by chiral HPLC analysis of the corresponding diacetate **III-14** (Daicel Chiralcel OD).

On the basis of these results, the author attempted to obtain both enantiomers of **III-3** by the combined use of commercially available (*S*)- and (*R*)-mandelic acids as shown in Scheme III-7. Crystallization and successive recrystallization of a diastereomeric salt mixture of rac-**III-3** with (*S*)-mandelic acid from ethanol gave diastereomerically pure (+)589-**III-15** in 35% yield. The combined filtrates of the crystallization and recrystallization were concentrated under reduced pressure to afford a solid mass, which gave (1*S*,2*R*)-enriched **III-3** on treatment with alkali. Crystallization of the salt of this (1*S*,2*R*)-enriched **III-3** with (*R*)-mandelic acid gave diastereomerically pure (–)589-**III-15** in 37% yield. From the filtrate, almost racemic **III-3** was recovered with no chemical deterioration nor significant loss, which could be used in the next resolution.

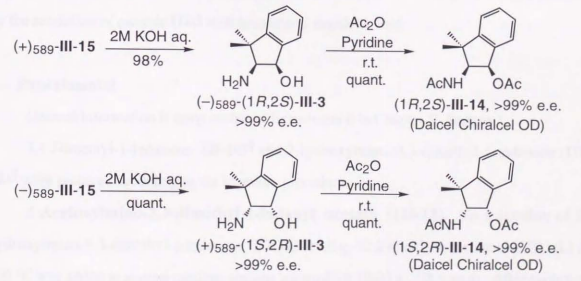
Treatment of (+)589-**III-15** and (–)589-**III-15** with alkali gave enantiomerically pure (–)589-(1*R*,2*S*)-**III-3** and (+)589-(1*S*,2*R*)-**III-3**, respectively in almost quantitative yield

(Scheme III-8). Thus, an efficient route to enantiomerically pure (−)589-(1*R*,2*S*)-**III-3** and (+)589-(1*S*,2*R*)-**III-3** was able to be developed.

Scheme III-7



Scheme III-8



The absolute configuration of (−)589-(1*R*,2*S*)-**III-3** was determined by a single-crystal X-ray structural analysis of salt (+)-**III-15**, which consisted of (−)589-(1*R*,2*S*)-**III-3** and (*S*)-mandelic acid (Fig. III-2). The absolute configuration of (−)589-(1*R*,2*S*)-**III-3** follows from the known absolute configuration of (*S*)-mandelic acid.

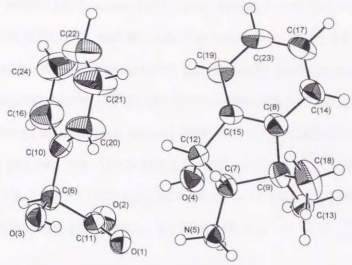


Figure III-2. ORTEP Drawing of (+)$_{589}$-**III-15**

In conclusion, an artificial chiral auxiliary, *cis*-2-amino-3,3-dimethyl-1-indanol **III-3** was designed, stereoselectively synthesized, and resolved. Racemic **III-3** was synthesized via *cis* selective reduction of 2-acetoxyimino-3,3-dimethyl-1-indanyl acetate **III-13**, which was derived from 3,3-dimethyl-1-indanone **III-10**. Both enantiomers of **III-3** were easily obtained by the resolution of racemic **III-3** with homochiral mandelic acid.

3. Experimental

General information is same as that of Experimental in Chapter II, Section 1.

3,3-Dimethyl-1-indanone (**III-10**)[4] and 2-hydroxyimino-3,3-dimethyl-1-indanone (**III-12**)[5] were prepared according to the literature procedures.

2-Acetoxyimino-3,3-dimethyl-1-indanyl acetate (III-13). To a solution of 2-hydroxyimino-3,3-dimethyl-1-indanone (**III-12**) (10.0 g, 52.8 mmol) in methanol (250 mL) at –20 °C was added in several portions sodium borohydride (9.00 g, 238 mmol). After evolution of gas had ceased, the solution was stirred at 0 °C for 3 h. The reaction mixture was poured into cold 1 M HCl aq. (300 mL), and the resulting mixture was stirred for 30 min. The mixture was added NaCl to saturate, and extracted with ether (5 × 200 mL). Usual workup gave a colorless solid (2-hydroxyimino-3,3-dimethyl-1-indanol), which was somewhat unstable to air-

exposure. Without further purification, this hydroxy oxime was treated with pyridine (200 ml) and acetic anhydride (100 mL), and this mixture was left to stand for 12 h. Then excess pyridine and acetic anhydride were evaporated, and the highly polar by-products were removed by short column chromatography (CH_2Cl_2). Evaporation of the eluent gave a slightly yellow solid, which was recrystallized from hexane (350 mL) to give **III-13** (12.5 g, 45.4 mmol, 86%) as colorless prisms: mp 114.0-114.5 °C; IR (KBr) 1764, 1738, 1660; ^{1}H-NMR ($CDCl_3$) δ 1.63 (3H, s), 1.69 (3H, s), 2.12 (3H, s), 2.33 (3H, s), 6.67 (1H, s), 7.20-7.56 (4H, m). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.30; H, 6.23; N, 5.10.

Racemic *cis*-2-Amino-3,3-dimethyl-1-indanol (rac-III-3). To a stirred solution of **III-13** (8.82 g, 32.0 mmol) in THF (50 mL) was added borane-THF complex (130 mL, 130 mmol; 1.0 M THF solution) to 0 °C. Then the reaction mixture was gradually heated and finally refluxed for 3 h. With cooling at 0 °C, 1 M HCl aq. (30 mL) was cautiously added to the mixture. After being stirred for 30 min, the mixture was basified to about pH 14 with 2 M KOH aq. and extracted with CH_2Cl_2 (5 × 200 mL). Usual workup gave rac-**III-3** (5.69 g, 32.0 mmol, 100%), which was sufficiently pure for further use.

An analytical sample was recrystallized from hexane/benzene (3/1) to give colorless prisms: mp 108.5-109.0 °C; IR (KBr) 3200, 2950, 1580, 995, 770; ^{1}H-NMR ($CDCl_3$) δ 1.21 (3H, s), 1.23 (3H, s), 1.80-2.50 (3H, br s), 3.21 (1H, br d), 4.93 (1H, br d), 7.19-7.43 (4H, m). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.33; H, 8.62; N, 7.90.

Resolution of rac-III-3.

(1*R*,2*S*)-2-Amino-3,3-dimethyl-1-indanol·(*S*)-mandelic acid salt ((+)589-III-15). To a solution of rac-**III-3** (5.28 g, 29.8 mmol) in ethanol (10 mL) was added (*S*)-mandelic acid (4.53 g, 29.8 mmol). To the resulting suspension of the diastereomeric salt mixture was added ethanol (60 mL), and the suspension was refluxed to dissolve the diastereomeric salt mixture completely. The clear solution was allowed to stand at rt for 1 h (from the point when the precipitation started), and then for 1 h at 0 °C. The precipitate was collected by filtration, and washed with cold ethanol (10 mL). Recrystallization of the

precipitate from ethanol (70 mL) under similar conditions gave diastereomerically pure (+)589-**III-15** (3.40 g, 10.3 mmol, 35% based on rac-**III-3** used) as colorless needles: $[\alpha]^{20.4}_{589}$ +38.3 (*c* 1.98, MeOH); mp 202.0-202.5 °C; IR (KBr) 3100, 1605, 1568, 1540, 760; ^{1}H-NMR (DMSO-d6) δ 1.20 (3H, s), 1.29 (3H, s), 3.34 (1H, d, *J*=6.2), 4.64 (1H, s), 5.00 (1H, d, *J*=6.2), 5.20-6.90 (5H, br), 7.15-7.49 (9H, m). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.13; H, 7.10; N, 4.16. X-ray crystallographic details: monoclinic, space group *C*2, *a*=21.778(2)Å, *b*=5.473(6)Å, *c*=16.417(2)Å, *V*=1770(3)Å^3, β=115.25(8)°, *R*=0.047, *Rw*=0.051.

To diastereomeric salt (+)589-**III-15** (20.0 mg, 0.0607 mmol), dissolved in pyridine (2 mL), was added acetic anhydride (1 mL), and the reaction mixture was allowed to stand for 12 h at rt. Then excess pyridine and acetic anhydride were evaporated, and the residue was purified by PTLC (ethyl acetate) to give (1*R*,2*S*)-2-acetamido-3,3-dimethyl-1-indanyl acetate ((1*R*,2*S*)-**III-14**) (15.8 mg, 0.0606 mmol, quant.) Chiral HPLC analysis (Daicel Chiralcel OD, hexane/2-propanol (9/1), α 1.38, shorter retention time for the 1*R*,2*S* isomer) of (1*R*,2*S*)-**III-14** indicated that (+)589-**III-15** was diastereomerically pure.

An analytical sample of (1*R*,2*S*)-**III-14** was recrystallized from hexane/benzene (9/1) to give colorless needles: $[\alpha]^{20.8}_{589}$ –170 (*c* 1.00, $CHCl_3$); mp 123.0-123.5 °C; IR (KBr) 3320, 1730, 1650; ^{1}H-NMR ($CDCl_3$) δ 1.22 (3H, s), 1.37 (3H, s), 2.07 (3H, s), 2.11 (3H, s), 4.66 (1H, dd, *J*=5.9, 9.9), 5.80 (1H, d, *J*=9.9), 6.04 (1H, d, *J*=5.9), 7.21-7.54 (4H, m). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33 N, 5.36. Found: C, 68.81; H, 7.39; N, 5.30.

(1*R*,2*S*)-2-Amino-3,3-dimethyl-1-indanol ((–)589-(1*R*,2*S*)-III-3). To a stirred suspension of (+)589-**III-15** (3.40 g, 10.3 mmol) in CH_2Cl_2 (100 mL) was added 2 M KOH aq. (200 mL). The mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). Usual workup of the combined organic layer and extracts gave (–)589-(1*R*,2*S*)-**III-3** (1.79 g, 10.1 mmol, 98%) as a colorless powder: $[\alpha]^{18.0}_{589}$ –16.8 (*c* 1.00, MeOH); mp 100.5-101.0 °C; IR (KBr) 3400, 2900, 1560, 1195, 758. The ^{1}H-NMR was identical with that of rac-**III-3**. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.67; H, 8.43; N, 8.20.

To amino alcohol (–)589-(1*R*,2*S*)-**III-3** (15.6 mg, 0.0880 mmol), dissolved in pyridine (2 mL), was added acetic anhydride (1 mL), and the reaction mixture was allowed to stand for 12 h at rt. Then excess pyridine and acetic anhydride were evaporated, and the residue was purified by PTLC (ethyl acetate) to give (1*R*,2*S*)-**III-14** (22.9 mg, 0.0876 mmol, quant.) Chiral HPLC analysis of (1*R*,2*S*)-**III-14** indicated that (–)589-(1*R*,2*S*)-**III-3** was enantiomerically pure.

(1*S*,2*R*)-2-Amino-3,3-dimethyl-1-indanol·(*R*)-mandelic acid salt ((–)589-III-15). The combined filtrates of the crystallization and recrystallization performed in order to obtain (+)589-**III-15**, were concentrated under reduced pressure to give a solid mass, which was treated with 2 M KOH aq. (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). Usual workup of the extracts gave (1*S*,2*R*)-enriched **III-3** (3.39 g, 19.1 mmol), which was treated with (*R*)-mandelic acid (2.91 g, 19.1 mmol) to give the diastereomeric salt mixture. Crystallization of this salt mixture from ethanol (70 mL) according to the procedure given for the preparation of (+)589-**III-15** gave diastereomerically pure (–)589-**III-15** (3.63 g, 11.0 mmol, 37%) as colorless needles: $[\alpha]^{20.8}_{589}$ –38.9 (*c* 2.08, MeOH). The other physical data were identical with those of (+)589-**III-15**. Chiral HPLC analysis of (1*S*,2*R*)-**III-14** ($[\alpha]^{20.8}_{589}$ +170 (*c* 1.00, $CHCl_3$); the other physical data were identical with those of (1*R*,2*S*)-**III-14**), derived from (–)589-**III-15** in a similar procedure to the preparation of (1*R*,2*S*)-**III-14**, indicated that (–)589-**III-15** was diastereomerically pure.

(1*S*,2*R*)-2-Amino-3,3-dimethyl-1-indanol ((+)589-(1*S*,2*R*)-III-3). According to the procedure given for the preparation of (–)589-(1*R*,2*S*)-**III-3**, (+)589-(1*S*,2*R*)-**III-3** (963 mg, 5.43 mmol, 100%) was obtained from (–)589-**III-15** (1.79 g, 5.43 mmol) as a colorless powder: $[\alpha]^{18.0}_{589}$ +16.7 (*c* 1.02, MeOH). The other physical data were identical with those of (–)589-(1*R*,2*S*)-**III-3**. Chiral HPLC analysis of (1*S*,2*R*)-**III-14**, derived from (+)589-(1*S*,2*R*)-**III-3** by similar procedure to that used in the preparation of (1*R*,2*S*)-**III-14**, indicated that (+)589-(1*S*,2*R*)-**III-3** was enantiomerically pure.

Detailes for X-ray structural analysis of (1*R*,2*S*)-2-Amino-3,3-dimethyl-1-indanol·(*S*)-mandelic acid salt ((+)589-III-15).

Chemical Formula	$C_{19}H_{23}NO_4$
Formula Weight	329.00
Crystal Size	0.50 × 0.15 × 0.05
a/Å	21.778 (2)
b/Å	5.4726 (6)
c/Å	16.417 (2)
β/degree	115.252 (8)
Volume of Unit Cell	1769.6 (1)
Crystal System	Monoclinic
Space Group	$C2$
Z value	4
D_{calc}/g cm^{-3}	1.23
Reflections used	1450
R;Rw	0.0470; 0.0511
Goodness of Fit	1.92
Maximum Shift/e. s. d. in final cycle	0.2333
Maximum Negative Peak in Final Diff. Map/e Å^{-3}	–0.26
Maximum Positive Peak in Final Diff. Map/e Å^{-3}	0.16

Fractional Atomic Coordinates & U(iso)

atom	x/a	y/b	z/c	U(iso)
O 1	-0.28220 (14)	-0.43200	-0.41699 (19)	0.053
O 2	-0.30457 (17)	-0.04336 (91)	-0.39890 (22)	0.062
O 3	-0.35808 (16)	-0.59713 (89)	-0.33551 (23)	0.060
O 4	-0.17063 (15)	0.14426 (89)	-0.35637 (22)	0.060
N 5	-0.17041 (17)	-0.28679 (94)	-0.44038 (23)	0.046
C 6	-0.3352 (2)	-0.3512 (11)	-0.3199 (3)	0.049

C 7	-0.11539 (19)	-0.25321 (102)	-0.34846 (26)	0.045
C 8	-0.01533 (19)	-0.04167 (110)	-0.25827 (26)	0.047
C 9	-0.04486 (19)	-0.18698 (94)	-0.34517 (30)	0.048
C 10	-0.2817 (2)	-0.3132 (11)	-0.2245 (3)	0.055
C 11	-0.30620 (18)	-0.26860 (108)	-0.38560 (25)	0.045
C 12	-0.1343 (2)	-0.0510 (13)	-0.2980 (3)	0.055
C 13	-0.0507 (2)	-0.0239 (11)	-0.4243 (3)	0.055
C 14	0.0521 (2)	0.0205 (13)	-0.2079 (3)	0.061
C 15	-0.0648 (2)	0.0368 (14)	-0.2331 (3)	0.063
C 16	-0.2838 (4)	-0.1124 (15)	-0.1761 (5)	0.090
C 17	0.0681 (3)	0.1681 (19)	-0.1327 (3)	0.090
C 18	-0.0037 (3)	-0.4130 (12)	-0.3454 (6)	0.090
C 19	-0.0495 (3)	0.1829 (26)	-0.1584 (4)	0.128
C 20	-0.2298 (4)	-0.4742 (18)	-0.1866 (4)	0.093
C 21	-0.1804 (5)	-0.4392 (21)	-0.0984 (5)	0.114
C 22	-0.1813 (4)	-0.2450 (20)	-0.0511 (4)	0.102
C 23	0.0184 (3)	0.2463 (27)	-0.1082 (4)	0.143
C 24	-0.2324 (5)	-0.0802 (19)	-0.0873 (5)	0.116
H 7	-0.113 (2)	-0.404 (9)	-0.316 (3)	0.041
H 5A	-0.212 (2)	-0.322 (10)	-0.436 (3)	0.043
H 13A	-0.077 (2)	0.123 (10)	-0.434 (3)	0.052
H 5B	-0.158 (2)	-0.422 (10)	-0.473 (3)	0.043
H 14	0.087 (2)	-0.027 (11)	-0.227 (3)	0.055
H 16	-0.317 (3)	0.007 (15)	-0.200 (4)	0.083
H 6	-0.378 (2)	-0.246 (10)	-0.331 (3)	0.047
H 13B	-0.003 (2)	0.045 (11)	-0.417 (3)	0.052
H 5C	-0.176 (2)	-0.152 (11)	-0.469 (3)	0.043
H 13C	-0.071 (2)	-0.119)10)	-0.484 (3)	0.052
H 12	-0.162 (2)	-0.103 (10)	-0.266 (3)	0.052
H 18A	-0.002 (3)	-0.514 (15)	-0.288 (4)	0.082
H 18B	-0.030 (3)	-0.513 (14)	-0.404 (4)	0.082
H 18C	0.040 (3)	-0.376 (13)	-0.337 (4)	0.082
H 3	-0.337 (3)	-0.674 (11)	-0.353 (3)	0.057
H 4	-0.209 (3)	0.148 (11)	-0.363 (3)	0.055
H22	-0.141 (3)	-0.211 (15)	0.016 (4)	0.091
H 23	0.029 (4)	0.359 (18)	-0.055 (5)	0.137
H 17	0.118 (3)	0.232 (15)	-0.095 (4)	0.084
H 19	-0.081 (4)	0.225 (19)	-0.139 (5)	0.124
H 24	-0.240 (4)	0.069 (16)	-0.055 (5)	0.106
H 21	-0.135 (3)	-0.561 (15)	-0.082 (4)	0.100

H 20	-0.230 (3)	-0.619 (13)	-0.216 (4)	0.081

Intramolecular bond length/Å (H omitted)

atom	atom	distance	atom	atom	distance
O1	--C11	1.252 (6)	O2	--C11	1.255 (8)
O3	--C6	1.421 (8)	O4	--C12	1.429 (8)
N5	--C7	1.485 (6)	C6	--C10	1.515 (6)
C6	--C11	1.532 (6)	C7	--C9	1.557 (6)
C7	--C12	1.540 (8)	C8	--C9	1.516 (7)
C8	--C14	1.386 (6)	C8	--C15	1.377 (7)
C9	--C13	1.536 (7)	C9	--C18	1.528 (8)
C10	--C16	1.368 (10)	C10	--C20	1.357 (10)
C12	--C15	1.509 (7)	C14	--C17	1.390 (9)
C15	--C19	1.381 (11)	C16	--C24	1.421 (11)
C17	--C23	1.373 (10)	C19	--C23	1.396 (11)
C20	--C21	1.400 (10)	C21	--C22	1.322 (14)
C22	--C24	1.357 (14)			

Intramolecular bond angles/degrees (H omitted)

atom	atom	atom	angle	atom	atom	atom	angle
O3	--C6	--C10	111.9 (5)	O3	--C6	--C11	111.8 (4)
C10	--C6	--C11	108.8 (4)	N5	--C7	--C9	114.9 (4)
N5	--C7	--C12	110.6 (4)	C9	--C7	--C12	107.5 (4)
C9	--C8	--C14	127.4 (4)	C9	--C8	--C15	111.9 (4)
C14	--C8	--C15	120.7 (5)	C7	--C9	--C8	99.8 (4)
C7	--C9	--C13	112.4 (4)	C7	--C9	--C18	112.5 (5)
C8	--C9	--C13	109.9 (5)	C8	--C9	--C18	114.4 (5)
C13	--C9	--C18	107.8 (5)	C6	--C10	--C16	120.6 (6)
C6	--C10	--C20	120.5 (6)	C16	--C10	--C20	118.9 (6)
O1	--C11	--O2	125.6 (4)	O1	--C11	--C6	116.7 (5)
O2	--C11	--C6	117.6 (5)	O4	-C12	--C7	112.0 (4)
O4	--C12	--C14	109.7 (6)	C7	--C12	--C15	101.0 (4)
C8	--C14	--C17	118.2 (5)	C8	--C15	--C12	111.5 (5)
C8	--C15	--C19	121.6 (5)	C12	--C15	--C19	126.9 (5)
C10	--C16	--C24	119.3 (8)	C14	--C17	--C23	120.8 (6)
C15	--C19	--C23	117.5 (7)	C10	--C20	--C21	120.5 (8)
C20	--C21	--C22	121.3 (9)	C21	--C22	--C24	119.5 (8)
C17	--C23	--C19	121.2 (9)	C16	--C24	--C22	120.4 (9)

4. References and Notes

1. Scholz and his co-workers have been reported this reaction affords **III-6** in 69% yield: Scholz, K. H.; Heine, H. G.; Hartmann, W. *Tetrahedron Lett.* **1978**, *17*, 1467.
2. Graham, S. H. *J. Chem. Soc.* (c) **1969**, 390.
3. Richter, H.; Schenck, M. German Patent, 1956; *No.* 940045.
4. Bosch, A.; Brown, A. K. *Can. J. Chem.* **1964**, *42*, 1718.
5. Koelsch, C. F.; LeClaire, C. D. *J. Org. Chem.* **1941**, *6*, 516.

Section II. Application of *cis*-2-Amino-3,3-dimethyl-1-indanol as a Precursor of Chiral Templates

1. Introduction

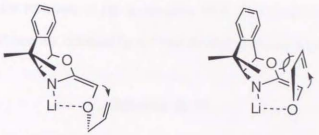
In Chapter III, Section I, the author described the design, synthesis, and resolution of a novel artificial chiral amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol (**III-3**). This amino alcohol has a structural characteristics that the orientation of the amino and hydroxyl groups is fixed and that the bulkiness of the two methyl substituents strongly influences the chiral environment near to the stereogenic center adjacent to the nitrogen atom. Then, the author expected that these structural features of this amino alcohol would function quite effectively when derived into its oxazoline- and oxazolidinone-type chiral templates. In this section, the author describes the applications of the oxazoline in the diastereoselective [2,3]-Wittig rearrangement, and of the chiral oxazolidinone in the diastereoselective reactions of the corresponding imide enolates with various electrophiles and in the asymmetric Diels-Alder reaction, respectively.

2. Results and Discussion

2.1. The Diastereoselective [2,3]-Wittig Rearrangement by Using a Chiral Oxazoline as a Chiral Template

In Chapter II, Section II, the author examined the diastereoselective [2,3]-Wittig rearrangement of allyl ether-type substrates, which contain a chiral oxazoline-type template derived from *cis*-2-amino-1-acenaphthenol. In these reactions, diastereomeric ratio was up to 82:18. In order to improve selectivity, the author intended to examine the diastereoselective [2,3]-Wittig rearrangement using a chiral oxazoline-type template, which was derived from *cis*-2-amino-3,3-dimethyl-1-indanol, with the expectation that the bulkiness of the two methyl groups would work effectively in diastereofacial discrimination in the reaction of the *E*-azaenolate with allyl terminus (**III-16** vs **III-17** in Fig. III-3).

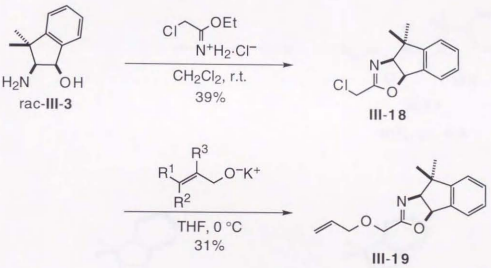
2-Chloromethyloxazoline **III-18**, synthesized from rac-**III-3** and imino ether hydrochloride, was allowed to react with potassium salt of allyl alcohol to give the corresponding 2-(allyloxy)methyloxazoline **III-19** (Scheme III-9).



III-16 **III-17**

Figure III-3. Supposed Structures of Azaenolates

Scheme III-9



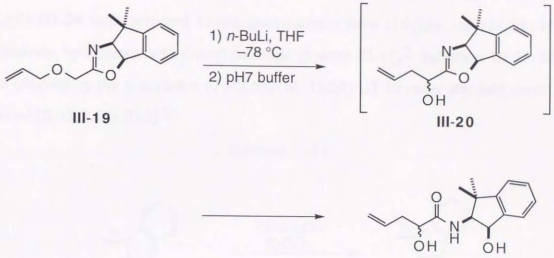
rac-**III-3** **III-18** **III-19**

The rearrangement of **III-19** was performed by using butyllithium as a base in THF at –78 °C (Scheme III-10). The homoallyl alcohol **III-20** obtained was somewhat unstable under slightly acidic conditions and a diastereomeric mixture of the corresponding amides **III-21** was obtained. This low stability of the product is considered to arise from the steric repulsion between the bulky substituent at the 2-position of the oxazoline moiety and the methyl substituents of the chiral template. Moreover, the diastereoselectivity was disappointingly lower (approximately 6:4, determined by ^{1}H-NMR analysis) than that observed in the reaction using the oxazoline-type template derived from *cis*-2-amino-1-acenaphthenol (d.r.=7:3).

Although it is not clear at present, ambiguity of the geometry of the azaenolate is supposed to be responsible to this low selectivity (Fig. III-4); *E*-azaenolate **III-22** and *Z*-azaenolate **III-23** were formed nearly equally, and, consequently, the both diastereomers were

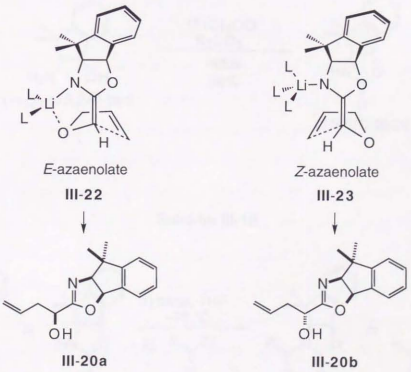
formed even though the reaction of the azaenolate with allyl terminus occurred at the less hindered diastereotopic face not shielded by the two methyl substituents of the template.

Scheme III-10



III-19 **III-20** **III-21**

61%, d.r.~6:4



E-azaenolate **III-22** *Z*-azaenolate **III-23**

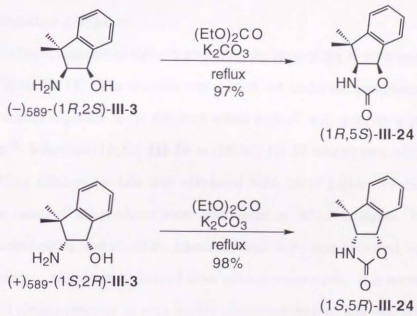
III-20a **III-20b**

Figure III-4. Transition State Models

2.2. Synthesis of Various *N*-Acyloxazolidinones

Since the oxazoline derived from **III-3** was found to be insufficient, the author considered to use **III-3** as a precursor for another chiral template, an oxazolidinone,[1] and applied it to several kinds of asymmetric reactions, such as the diastereoselective alkylation of the corresponding *N*-acyloxazolidinones. The homochiral oxazolidinones (1*R*,5*S*)- and (1*S*,5*R*)-**III-24** were prepared almost quantitatively from (1*R*,2*S*)- and (1*S*,2*R*)-**III-3**, respectively, by treatment with diethyl carbonate (Scheme III-11).[2] Substrates **III-25**~**III-30** were obtained by the *N*-acylation of (1*R*,5*S*)- or (1*S*,5*R*)-**III-24** under standard conditions (Scheme III-12, Table III-3).[2]

Scheme III-11



Scheme III-12

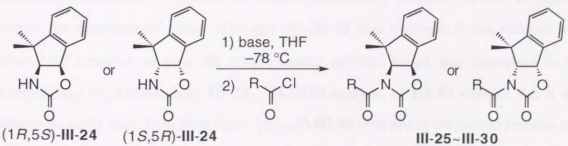


Table III-3. Yields of *N*-Acyloxazolidinones

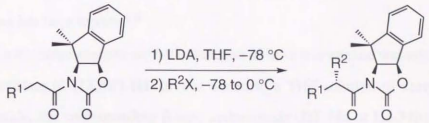
entry	config. of **III-24**	base	R	product	yield/%
1	1*S*,5*R*	*n*-BuLi	Me	(1*S*,5*R*)-**III-25**	95
2	1*R*,5*S*	*n*-BuLi	Et	(1*R*,5*S*)-**III-26**	95
3	1*S*,5*R*	*n*-BuLi		(1*S*,5*R*)-**III-26**	97
4	1*R*,5*S*	*n*-BuLi	$PhCH_2CH_2$	(1*R*,5*S*)-**III-27**	quant.
5	1*R*,5*S*	*n*-BuLi	$PhCH_2$	(1*S*,5*R*)-**III-28**	83
6	1*R*,5*S*	MeMgBr		(1*R*,5*S*)-**III-29**	53
7	1*R*,5*S*	MeMgBr	Me 	(1*R*,5*S*)-**III-30**	95

2.3. Diastereoselective Alkylation

The alkylation reaction of the corresponding enolates of the *N*-acyloxazolidinones was examined (Scheme III-13). The reaction was carried out under the conditions, which Evans and his co-workers reported to be the best when valinol was used as a precursor of an oxazolidinone.[3] Substrate (1*R*,5*S*)-**III-26** or (1*R*,5*S*)-**III-27** was treated with LDA in THF, and the resulting lithium enolate was alkylated with alkyl halides (Table III-4). The diastereomeric ratios of the products were determined by HPLC analysis. In all cases, the reaction proceeded easily, and excellent diastereoselectivities were observed, superior to those obtained by using oxazolidinones derived from natural compounds. It is noteworthy that the asymmetric alkylation reaction is very highly diastereoselective and that the selectivity is maintained even in the methylation, which usually results in poor selectivity. Furthermore, removal of the oxazolidinone template was easily achieved by hydrolysis of the products with aqueous LiOOH;[2] for example, hydrolysis of **III-31c** gave (–)589-(*R*)-**III-32** and oxazolidinone-auxiliary (1*R*,5*S*)-**III-24** almost quantitatively (Scheme III-14). In order to examine the enantiomeric purity of (–)589-(*R*)-**III-32** thus obtained, it was reduced with borane-THF complex to give the corresponding alcohol, which was converted to the corresponding (+)-MTPA ester **III-33**. ^{1}H-NMR analysis of **III-33** showed that it was diastereomerically pure, indicating that (–)589-(*R*)-**III-32** obtained in the present reaction was almost enantiomerically pure and that no epimerization occurred under the conditions of

hydrolysis. The absolute configuration of **III-31c** was determined on the basis of the absolute configuration of **III-32**. The absolute configurations of the other major products of the present reactions were correlated with that of **III-31c** by comparing their ^{1}H-NMR spectral and HPLC data.

Scheme III-13



(1*R*,5*S*)-**III-26** (R^1=Me)
(1*R*,5*S*)-**III-27** (R^1=Bn)

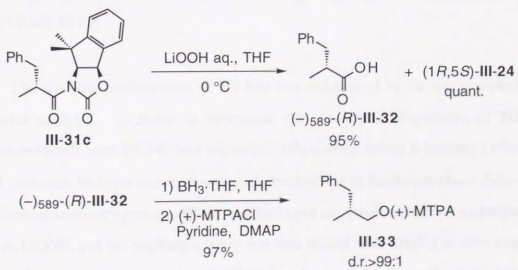
III-31

Table III-4. Alkylation of *N*-Acyloxazolidinones

entry	R^1	R^2X	product	yield/%[a]	d.r.[b]
1	Me	EtI	**III-31a**	57	>99:1
2	Me	AllylBr	**III-31b**	95	>99:1
3	Me	BnBr	**III-31c**	quant.	>99:1
4	Bn	MeI	**III-31d**	83	97:3

[a] Isolated yield of major product. [b] Determined by HPLC analysis.

Scheme III-14

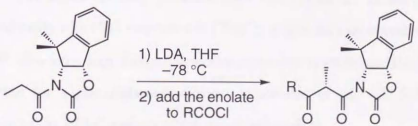


2.4. Diastereoselective Acylation, Bromination, and Hydroxylation

The author next applied the chiral enolates to other diastereoselective reactions, such as acylation, bromination, and hydroxylation. These types of reactions have been investigated by Evans and his co-workers using oxazolidinone-type auxiliaries derived from natural chiral compounds.[5-7] However, in spite of the quite significant synthetic utility of these reactions, no further investigation on improvement of the stereoselectivities by designing new oxazolidinones has been reported.[8]

First, a diastereoselective acylation reaction of the imide enolate was attempted. When the lithium enolate of (1*S*,5*R*)-**III-26** was added to a THF solution of acetyl chloride or benzoyl chloride, the corresponding β-keto carboximide (**III-34a** or **III-34b**) was obtained with excellent diastereoselectivity (Scheme III-15); the selectivity (d.r. ≥98:2) is better than that reported by Evans and his co-workers for the acylation of valinol- and norephedrine-derived *N*-propionyloxazolidinones (d.r. up to 96:4).[5] The newly created asymmetric centers of these acylated products were not affected during its purification by chromatography or recrystallization, while they were slowly epimerized under basic conditions (1M Et_3N, CH_2Cl_2, room temperature), as was reported.[5]

Scheme III-15



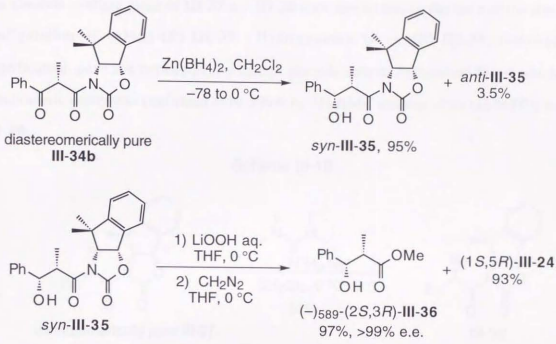
(1*S*,5*R*)-**III-26**

III-34a (R=Me): 89%, d.r.=98:2
III-34b (R=Ph): 86%, d.r.>99:1

The absolute configuration of **III-34a** was determined by its single-crystal X-ray structural analysis. In order to determine the absolute configuration of **III-34b**, diastereomerically pure **III-34b** was converted to the corresponding β-hydroxy carboximide **III-35** (*syn*:*anti*=96:4) by treatment with zinc borohydride in dichloromethane (Scheme III-16). Diastereomerically pure *syn*-**III-35**, obtained upon recrystallization, was hydrolyzed with aqueous LiOOH, and the resulting mixture was then treated with CH_2N_2 in ether to give the known β-hydroxy ester (–)589-(2*S*,3*R*)-**III-36**,[2] and oxazolidinone-auxiliary (1*S*,5*R*)-**III-24**

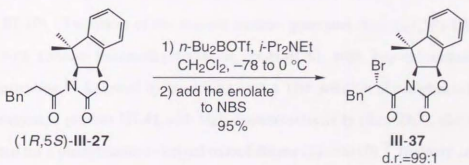
in good yields. The absolute configurations of **III-34b** and *syn*-**III-35** were determined on the basis of the absolute configuration of (–)$_{589}$-(2*S*,3*R*)-**III-36**. The enantiomeric purity of (–)$_{589}$-(2*S*,3*R*)-**III-36** was found to be >99% e.e. by chiral HPLC analysis (Daicel Chiralcel OJ).

Scheme III-16



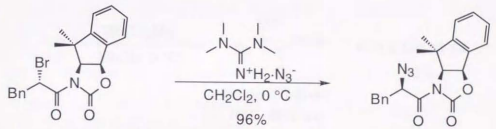
The boron enolate, generated from (1*R*,5*S*)-**III-27** by the Mukaiyama method,[10] reacted easily with NBS suspended in CH_2Cl_2 to give the corresponding α-bromo carboximide **III-37** with very high diastereoselectivity (d.r.=99:1) (Scheme III-17), also better than that reported for a phenylalaninol-derived oxazolidinone (d.r.=95:5).[6] The selectivity was determined by HPLC analysis of the unpurified product.

Scheme III-17

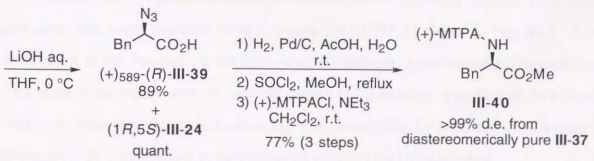


Diasteromerically pure **III-37**, easily purified by chromatography, was treated with 1,1,3,3-tetramethylguanidinium azide,[6,11] to give the corresponding α-azido caboximide **III-38** (almost complete inversion at the stereogenic center was observed), which was then hydrolyzed with lithium hydroxide to give α-azido acid (+)$_{589}$-(*R*)-**III-39**[6] in good yield, along with quantitative recovery of oxazolidinone auxiliary (1*R*,5*S*)-**III-24** (Scheme III-18). The absolute configurations of **III-37** and **III-38** were determined on the basis of the absolute configuration of (+)$_{589}$-(*R*)-**III-39**. Hydrogenation of (+)-(*R*)-**III-39**, followed by esterification, gave the corresponding methyl phenylalaninate hydrochloride, of which the enantiomeric purity was confirmed to be >99% by ^{1}H-NMR analysis of its (+)-MTPA amide **III-40**.

Scheme III-18



diastreomerically pure **III-37** **III-38**

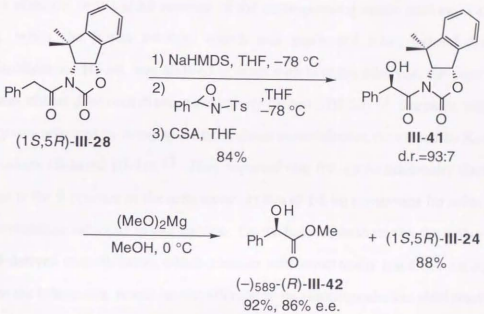


III-40
>99% d.e. from diastereomerically pure **III-37**

Finally, a diastereoselective hydroxylation reaction of the imide enolate was examined (Scheme III-19). Treatment of the sodium enolate, generated from (1*S*,5*R*)-**III-28** by the reaction with sodium hexamethyldisilazide (NaHMDS), with 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine,[12] followed by quenching with a THF solution of camphorsulfonic acid, gave hydroxylated product **III-41** with high diastereoselectivity (d.r.=93:7), also better than that reported for a phenylalaninol-derived oxazolidinone (d.r.=90:10).[7] Hydroxy imide **III-41** was treated with magnesium methoxide to give (*R*)-methyl mandelate (**III-42**) and

oxazolidinone-auxiliary (1*S*,5*R*)-**III-24** in 92 and 88% yields, respectively. The absolute configuration and enantiomeric purity of **III-42** were determined by chiral HPLC analysis (Daicel Chiralcel OJ). The absolute configuration of **III-41** was determined on the basis of the absolute configuration of **III-42**.

Scheme III-19



The absolute configurations of the products obtained in the present reactions are in good agreement with those expected from a chelate model **III-43** shown in Fig. III-5. The conformation of the *Z*-enolate relative to the oxazolidinone part would be defined by chelation of the metal of the enolate with the carbonyl oxygen of the auxiliary regardless of the kind of metal used. Thus, the reaction of the *Z*-enolate with electrophiles occurred at the less hindered diastereotopic face not shielded by the two methyl groups of the chiral template.

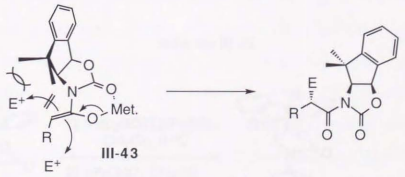
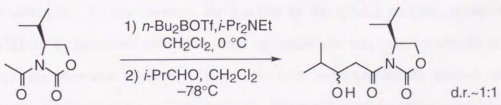


Figure III-5. Structure of Chiral Imide Enolate

2.5. The Diastereoselective Aldol Condensation Reaction of *N*-Acetyloxazolidinone

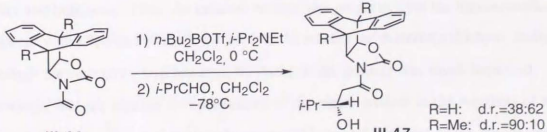
Asymmetric aldol reaction is one of the most important methods to obtain non-racemic compounds. Among the various methods developed so far, utilization of chiral oxazolidinone as a chiral template, which was originally developed by Evans and his co-workers, has been widely applied as a most reliable method. However, this oxazolidinone-type template is known to be less effective in the aldol reaction of the corresponding acetic acid equivalent. For example, when the boron enolate, which was generated from valinol-derived *N*-acetyloxazolidinone **III-44**, was allowed to react with isobutyraldehyde, the corresponding product was obtained without diastereoselectivity (Scheme III-20).[13] Recently, much higher selectivity was achieved by using an artificial chiral oxazolidinone, developed by Kunieda and his co-workers (Scheme III-21).[13] They reported that the conformationally fixed methyl substituent at the 9-position of the anthracene skelton of **III-46** is essential for achieving high level of asymmetric induction in this reaction. On the basis of these results, the author expected that **III-3**-derived oxazolidinone, which contains conformationally fixed two methyl groups attached to the indane ring, would be also effective in the diastereoselective aldol reaction of the corresponding acetic acid equivalent (Fig. III-6).

Scheme III-20



III-44 **III-45**

Scheme III-21



III-46 **III-47**

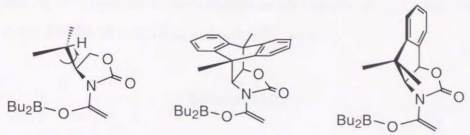
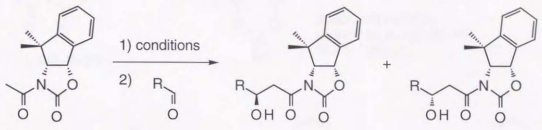


Figure III-6. Supposed Structures of Enolates

The aldol reactions of various kinds of the enolates, generated from (1*S*,5*R*)-**III-25**, with isobutyraldehyde and benzaldehyde were investigated (Scheme III-22). The results are shown in Table III-5. The diastereoselectivity was determined by HPLC analysis. When the boron enolate, generated from (1*R*,5*S*)-**III-25** by the Mukaiyama method,[2,10] was allowed to react with isobutyraldehyde (entry 1), the observed diastereoselectivity (d.r.=82:18) was much better than that reported for a valinol-derived oxazolidinone (d.r.=57:43).[2] The titanium enolate, which was generated from (1*S*,5*R*)-**III-25** by treatment with $TiCl_4$ and *i*-Pr_2NEt, reacted successfully with isobutyraldehyde to give the product with better selectivity (entry 2). However, the selectivity in the reactions of these enolates with benzaldehyde were disappointingly low, presumably because of relatively high reactivities of both these enolates and benzaldehyde. To the contrary, the reaction of the lithium enolate, generated from (1*S*,5*R*)-**III-25** by treatment with LDA, with benzaldehyde was quite successful and good selectivity was observed. However, its reaction with isobutyraldehyde resulted in failure because of its relatively low reactivity (entry 3). The reaction of the titanium enolate, which was generated by treatment of the lithium enolate with $ClTi(i\text{-}PrO)_3$, with isobutyraldehyde afforded the products with excellent selectivity, but its reactivity was still insufficient (entry 4). The author considered that the low reactivity of this enolate was arised from its low Lewis acidity and bulkiness. Then, the titanium enolate was prepared from the lithium enolate by treatment with $Cl_2Ti(i\text{-}PrO)_2$[14] and used in the reaction with isobutyraldehyde (entry 5). Although the selectivity was lowered, the yield of the product was much improved. It is noteworthy that the relative stereochemistry of the major product in the reactions of these titanium enolates with isobutyraldehyde, generated by metal exchange of the lithium enolate

(entries 4 and 5), were opposite to that obtained in the reaction of the enolate generated by treatment of (1*S*,5*R*)-**III-25** with $TiCl_4$ and *i*-Pr_2NEt (entry 2).

Scheme III-22



(1*S*,5*R*)-**III-25** **III-51** **III-52**

Table III-5. The Diastereoselective Aldol Reactions of *N*-Acetyloxazolidinone (1*S*,5*R*)-**III-25** Under Various Conditions

entry	conditions			yield/% (**III-51**:**III-52**[a])	
	reagents	solv.	temp./ °C	R=*i*-Pr	R=Ph
1	*n*-Bu_2BOTf, *i*-Pr_2NEt	CH_2Cl_2	–78 to 0	75 (82:18)	72 (59:41)
2	$TiCl_4$, *i*-Pr_2NEt	CH_2Cl_2	–78	57 (88:12)	80 (36:64)
3	LDA	Et_2O	–78	n.r.	95 (88:12)
4	LDA then $ClTi(Oi\text{-}Pr)_3$	Et_2O	–78 to 0	12 (3:97)	74 (18:82)
5	LDA then $Cl_2Ti(Oi\text{-}Pr)_2$	Et_2O	–78	78 (28:72)	–

[a] Determined by HPLC analysis.

On the basis of these results, the author carried out the aldol reactions with various aldehydes with properly using titanium enolates **III-53** and **III-54** (directly generated by treatment with $TiCl_4$ and *i*-Pr_2NEt, and generated by metal exchange of the lithium enolate, respectively) and the lithium enolate **III-55** (Scheme III-23, Table III-6). The reaction of titanium enolate **III-53** with heptanal was successful (entry 1), whereas the reaction with pivalaldehyde proceeded only slowly to give the diastereomeric mixture with low yield and selectivity (entry 3). Several attempts to improve the selectivity in this reaction revealed that the use of the titanium enolate **III-54** is most suitable (entry 4).

Scheme III-23

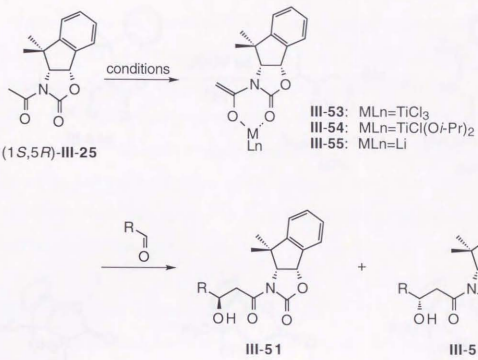


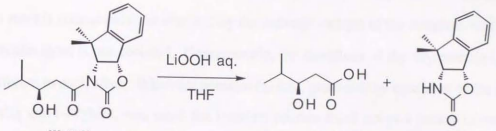
Table III-6. The Diastereoselective Aldol Reactions of *N*-Acetyloxazolidinone with Various Aldehydes

entry	R	conditions[a]	enolate	yield/%	**III-51**:**III-52**[b]
1	*n*-Hex	A	**III-53**	68	74:26
2	*i*-Pr	A	**III-53**	57	88:12
3	*t*-Bu	A	**III-53**	13	41:59
4	*t*-Bu	B	**III-54**	79	17:83
5	Ph	C	**III-55**	95	88:12

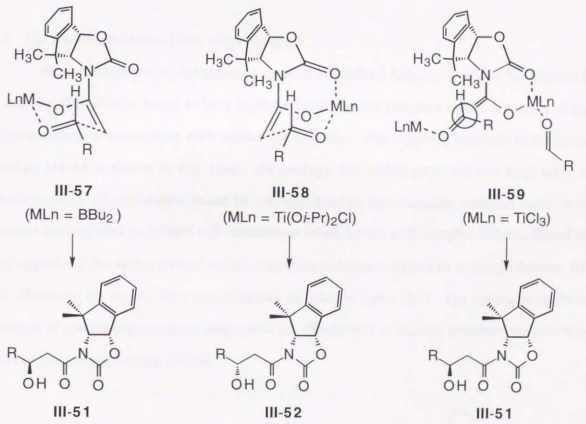
[a] Conditions A: $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, –78 °C. Conditions B: LDA, Et_2O then $Cl_2Ti(O$*i*-$Pr)_2$, –78 °C. Conditions C: LDA, Et_2O, –78 °C. [b] Determined by HPLC analysis.

Hydrolysis of **III-51b** gave (+)589-(*R*)-**III-56** and oxazolidinone-auxiliary (1*R*,5*S*)-**III-24** (Scheme III-24). The absolute configuration of **III-51b** was determined on the basis of the absolute configuration of (+)589-(*R*)-**III-56**.[6c, 13] The absolute configurations of the other major products of the present reactions were correlated with that of **III-51b** by comparing their ^{1}H-NMR spectral and HPLC data.

Scheme III-24



III-51b (+)$_{589}$-(*R*)-**III-56** 90% (1*S*,5*R*)-**III-24** quant.



III-57 (MLn = BBu_2) **III-58** (MLn = $Ti(O\text{-}iPr)_2Cl$) **III-59** (MLn = $TiCl_3$)

III-51 **III-52** **III-51**

Figure III-7. Transition State Models

The stereochemistries of the major products obtained in the reactions of various enolates are explained by the transition state models shown in Fig. III-7. When the boron enolate and the titanium enolate generated by metal exchange were used, the reactions are considered to proceed via 6-membered rings of chair conformation as shown as **III-57** and **III-58**,

respectively. These 6-membered rings are considered to be formed in the side of the diastereoface, and away from the two methyl groups of the template.[2,13] In **III-58**, the titanium atom is considered to be chelated by the carbonyl oxygen of the template, whilst in **III-57**, the boron atom is not chelated. Consequently, the directions of the asymmetric induction were different to each other. When the titanium enolate, generated by treatment of the substrate with $TiCl_4$ and *i*-Pr_2NEt, was used, the titanium enolate itself act as a strong Lewis acid to activate aldehyde. This activated aldehyde is considered to react with another enolate via open chain transition state model **III-59** to give the major product of the relative configuration, which is different from that of the major product obtained in the reaction of the titanium enolate generated by metal exchange.

2.6. The Diastereoselective Diels-Alder Reaction

As mentioned above, the chiral oxazolidinone derived from *cis*-2-amino-3,3-dimethyl-1-indanol (**III-3**) was found to be a highly effective chiral template in the reactions of the corresponding imide enolates with various electrophiles. The supposed structure of the imide enolate **III-43** is shown in Fig. III-8. By analogy, the author expected that high level of diastereofacial discrimination could be accomplished in the conjugate addition reaction of various nucleophiles to a chiral α,β-unsaturated imide-Lewis acid complex **III-60**. Based on this hypothesis the author carried out the conjugate addition reactions as shown in Scheme III-25. However, the results were unsatisfactory as listed in Table III-7. The conjugate addition reaction of several organocupper reagents to **III-30** was also examined, however, the reactions did not proceeded (Scheme III-26).

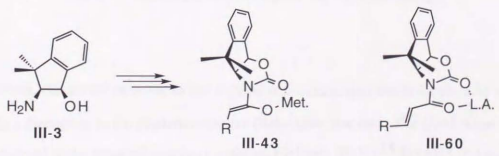
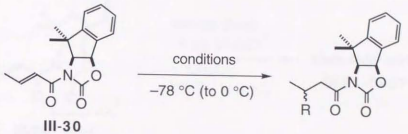


Figure III-8. Supposed Structures of Imide-enolate **III-43** and α,β-Unsaturated Imide-Lewis acid Complex **III-60**

Scheme III-25

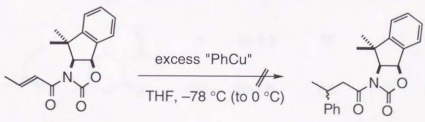


III-30

Table III-7. Conjugate addition Reaction to **III-30**

entry	conditions	R	yield/%	d.r.
1	4eq. Et_2AlCl, toluene	Et	87	75:25
2	TMS , $TiCl_4$ CH_2Cl_2, –78 °C	Allyl	64	72:28
3	$BnONH_2$, Et_2AlCl CH_2Cl_2, –78 °C	BnONH	0	–

Scheme III-26

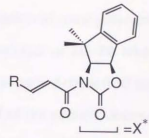


III-30

"PhCu" = $Ph_2CuMgBr{\cdot}MgBrI$, $Ph_2CuLi{\cdot}LiI$, PhMgBr+cat. CuI

Next, the author intended to use a chiral α,β-unsaturated imide-Lewis acid complex **III-60** as a dienophile in the diastereoselective Diels-Alder reaction. The Diels-Alder reaction was performed under standard reaction conditions (Scheme III-27);[15] Et_2AlCl (1.4 equivalent to the substrate) and CH_2Cl_2 were used as activator and solvent, respectively. The results are listed in Table III-8.

Scheme III-27

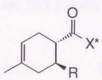
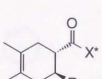


III-29: R=H
III-30: R=Me

excess diene
1.4 eq. Et_2AlCl
CH_2Cl_2
−78 °C (to 0 °C)

Diels-Alder adduct
III-61~**III-67**

Table III-8. Diastereoselective Diels-Alder Reaction of *N*-(α,β-Unsaturated acyl) oxazolidinone with Various Dienes

entry	diene	major diastereomer	R	adduct	yield/%	*endo* :*exo*[a]	d.r.[a]
1			H	**III-61**	75	97:3	98:2[b]
2			Me	**III-62**	97	99:1	>99:1[b]
3			H	**III-63**	44	99:1	99:1[b]
4[c]			Me	**III-64**	58	98:2	96:4[b]
5[c]			H	**III-65**	76	–[d]	>99:1
6[c]			Me	**III-66**	65	–[d]	>99:1
7[c]			H	**III-67**	33	–	98:2
8[c]			Me	–	0[e]	–	–

[a] Determined by HPLC. [b] D.r. of the *endo*-adduct. [c] The reaction temperature was allowed to raise to 0 °C. [d] The regio-isomeric ratio, determined by HPLC analysis, was >99:1. [e] The products were complicated.

Excellent diastereofacial selectivity and *endo*/*exo* selectivity (or regio selectivity) were achieved. It is noteworthy that the diastereofacial selectivities were excellent even in the reactions of *N*-acryloyloxazolidinone **III-29** (entries 1,3,5,7). Furthermore, the diastereofacial

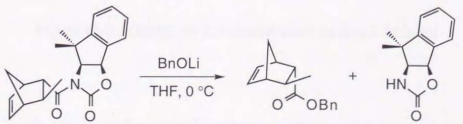
selectivities were also excellent in the reactions with acyclic dienes (entries 5-7). The reaction with a relatively less reactive diene required raising the temperature to 0 °C (entries 4-8), which led to formation of some polymeric substances as by-products, along with the desired product. The cycloadduct of **III-30** with 2,3-dimethylbutadiene was not obtained even when the reaction was carried out at 0 °C for 5 h (entry 8).

All of the adducts obtained in the present reactions were crystalline due to the high crystallizability of the template part. This enabled the author to obtain the products diastereomerically pure after a single recrystallization. For example, recrystallization of the diastereomeric mixture, obtained by the reaction of **III-30** with cyclohexadiene (entry 4), from hexane gave the corresponding diasteromerically pure cycloadduct **III-64** in 73% yield.

Removal of the template was easily accomplished by alcoholysis of the product (Scheme III-28).[15] For example, treatment of diastereomerically pure **III-62** with lithium phenylmethoxide in THF gave the corresponding ester (+)$_{589}$-**III-68** and the oxazolidinone-template **III-24** in excellent yields.

The absolute configuration of (+)$_{589}$-**III-68** was determined by a comparison of its sign of the optical rotation with that in the literature.[15] The absolute configuration of **III-62** was determined on the basis of the absolute configuration of (+)$_{589}$-**III-68**, and those of the other major products of the present reactions were correlated with that of **III-62** by comparing their ^{1}H-NMR spectral and HPLC data.

Scheme III-28



III-62 (+)$_{589}$-**III-68** 93% (1*R*,5*S*)-**III-24** 95%

2.7. Further Seeking for a More Efficient Template

From the results as described above, a chiral oxazolidinone derived from *cis*-2-amino-3,3-dimethyl-1-indanol (**III-3**) was found to be a quite efficient chiral template for various diastereoselective reactions. However, in some cases such as the aldol reaction of the correponding acetic acid equivalent and the conjugate addition to the correponding α,β-unsaturated imide, further improvement of selectivity is desired. The author considers that attachment of more bulky substituents at 3-position of the indane ring of the template is a quite suitable design of the auxilary with better selectivity; the bulky substituents at 3-position would be able to more efficiently shield the diastereoface of the correponding enolate and β-carbon of the correponding α,β-unsaturated imide (Fig. III-9).

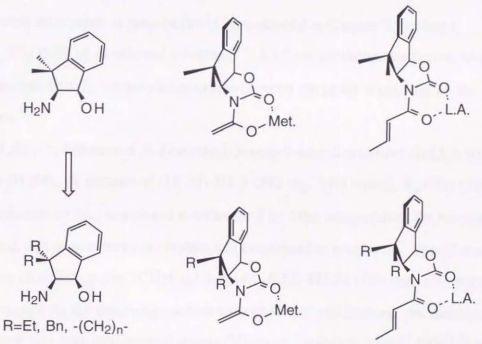


Figure III-9. Design of 3,3-Dialkyl-*cis*-2-amino-1-indanol

In conclusion, an artificial chiral auxiliary, *cis*-2-amino-3,3-dimethyl-1-indanol was used as a precursor of chiral oxazoline- and oxazolidinone-type templates. The oxazoline was applied to the diasteroselective [2,3]-Wittig rearrangement, however, it was not so efficient as *cis*-2-amino-1-acenaphthenol-derived one. The oxazolidinone was a quite effective chiral template in the diastereoselective reactions of the corresponding chiral imide enolates with

various electrophiles and in the diastereoselective Diels-Alder reaction. This new chiral oxazolidinone has several favorable characteristics: 1) It induces stereoselectivity more effectively than usually used chiral oxazolidinones derived from naturally occurring compounds. 2) All of the reaction products obtained here were crystalline due to the high crystallizability of the auxiliary moiety. Therefore, it is possible to obtain the compounds in high enantiomeric purity after a single recrystallization, when necessary. 3) Both enantiomers of the oxazolidinone were easily and equally available. Therefore, enantiopure compound with desired absolute configuration can be synthesized by using properly each enantiomer of the auxiliary.

3. Experimental

General information is same as that of Experimental in Chapter II, Section 1.

$Zn(BH_4)_2$ (0.14 M ethereal solution),[9] 1,1,3,3-tetramethylguanidinium azide,[11] and 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine[12] were prepared according to the literature procedures.

(1*R*,5*S*)-7,8-Benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane ((1*R*,5*S*)-III-24). A mixture of (1*R*,2*S*)-**III-3** (542 mg, 3.06 mmol), K_2CO_3 (30 mg) and diethyl carbonate (4 mL) was stirred at reflux for 7 h. After being cooled, the reaction mixture was filtered, and excess diethyl carbonate was evaporated to give an oil. The oil was purified by column chromatography (CH_2Cl_2) to give (1*R*,5*S*)-**III-24** (603 mg, 2.97 mmol, 97%), which was used for the following reaction without further purification. An analytical sample was recrystallized from hexane/ethyl acetate (3/1) to give colorless prisms: $[\alpha]^{20.4}_{589}$ +179 (*c* 5.00, $CHCl_3$); mp 124.5-125.0 °C; IR (KBr) 3280, 1750, 1718; ^{1}H-NMR ($CDCl_3$) δ 1.18 (3H, s), 1.34 (3H, s), 4.24 (1H, d, *J*=6.8), 5.96 (1H, d, *J*=6.8), 6.6-6.7 (1H, br s), 7.16-7.49 (4H, m). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.87; H, 6.38; N, 6.73.

(1*S*,5*R*)-7,8-Benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane ((1*S*,5*R*)-III-24). According to the procedure given for the preparation of (1*R*,5*S*)-**III-24**, (1*S*,5*R*)-**III-24** (1.13 g, 5.54 mmol, 98%) was obtained from (1*S*,2*R*)-**III-3** (1.00 g, 5.64

mmol) as colorless prisms: $[\alpha]^{22.6}_{589}$ –180 (*c* 5.10, $CHCl_3$). The other physical data were identical with those of (1*R*,5*S*)-**III-24**.

***N*-Acetyl-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo [3.3.0]octane ((1*S*,5*R*)-III-25).** To a solution of (1*S*,5*R*)-**III-24** (500 mg, 2.50 mmol) in THF (5.0 mL) was added butyllithium (1.70 mL, 2.70 mmol; 1.60 M hexane solution) at –78 °C, and the mixture was stirred for 10 min at –78 °C. To this solution was added acetyl chloride (0.24 mL, 2.7 mmol) at –78 °C, and the mixture was stirred at –78 °C for 30 min and then at 0 °C for 30 min. The reaction was quenched by adding saturated NH_4Cl aq. (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL). Usual workup gave a colorless solid, which was purified by column chromatography (hexane/ethyl acetate (9/1)) to give (1*S*,5*R*)-**III-25** (580 mg, 2.40 mmol, 94%) as colorless crystals, which was used in the following reaction without further purification. An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]^{22.8}_{589}$ –378 (*c* 5.06, $CHCl_3$); mp 109.0-110.0 °C; IR (KBr) 1775, 1700; ^{1}H-NMR ($CDCl_3$) δ 1.14 (3H, s), 1.56 (3H, s), 2.60 (3H, s), 4.84 (1H, d, *J*=7.9), 5.79 (1H, d, *J*=7.9), 7.26-7.49 (4H, m).

***N*-Propionyl-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo [3.3.0]octane ((1*R*,5*S*)-III-26).** According to the procedure given for the preparation of (1*S*,5*R*)-**III-25**, (1*R*,5*S*)-**III-26** (370 mg, 1.43 mmol, 95%) was obtained from (1*R*,5*S*)-**III-24** (306 mg, 1.51 mmol) as colorless needles, which was used in the following reaction without further purification. An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]^{22.4}_{589}$ +366 (*c* 5.00, $CHCl_3$); mp 98.5-99.0 °C; IR (KBr) 1760, 1700; ^{1}H-NMR ($CDCl_3$) δ 1.13 (3H, s), 1.22 (3H, t, *J*=7.9), 1.57 (3H, s), 2.90-3.18 (2H, m), 4.85 (1H, d, *J*=7.8), 5.79 (1H, d, *J*=7.8), 7.20-7.57 (4H, m). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.55; N, 5.24.

***N*-Propionyl-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo [3.3.0]octane ((1*S*,5*R*)-III-26).** According to the procedure given for the preparation of (1*S*,5*R*)-**III-25**, (1*S*,5*R*)-**III-26** (621 mg, 2.40 mmol, 97%) was obtained from (1*S*,5*R*)-**III-24** (500 mg, 2.46 mmol) as colorless needles: $[\alpha]^{22.4}_{589}$ –364 (*c* 4.05, $CHCl_3$). The other physical data were identical with those of (1*R*,5*S*)-**III-26**.

***N*-(3-Phenylpropionyl)-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane ((1*R*,5*S*)-III-27).** According to the procedure given for the preparation of (1*S*,5*R*)-**III-25**, from (1*R*,5*S*)-**III-24** (271 mg, 1.33 mmol) and 3-phenylpropionyl chloride (0.27 g, 1.6 mmol), (1*R*,5*S*)-**III-27** (446 mg, 1.33 mmol, 100%) was obtained as a colorless solid. An analytical sample was recrystallized from hexane/benzene (19/1) to give colorless prisms: $[\alpha]^{21.4}_{589}$ +254 (*c* 3.30, $CHCl_3$); mp 97.5-98.0 °C; IR (KBr) 1778, 1692; ^{1}H-NMR ($CDCl_3$) δ 1.08 (3H, s), 1.55 (3H, s), 2.97-3.07 (2H, m), 3.23-3.39 (2H, m), 4.83 (1H, d, *J*=7.8), 5.76 (1H, d, *J*=7.8), 7.18-7.55 (9H, m). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.04; H, 6.25; N, 3.92.

***N*-Phenylacetyl-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane ((1*S*,5*R*)-III-28).** According to the procedure given for the preparation of (1*S*,5*R*)-**III-25**, from (1*S*,5*R*)-**III-24** (500 mg, 2.46 mmol) and phenylacetyl chloride (0.46 g, 2.9 mmol), (1*S*,5*R*)-**III-28** (656 mg, 2.04 mmol, 83%) was obtained as a colorless solid. An analytical sample was recrystallized from hexane/benzene (19/1) to give colorless prisms: $[\alpha]^{22.4}_{589}$ –331 (*c* 2.11, $CHCl_3$); mp 117.5-118.0 °C; IR (KBr) 1780, 1700; ^{1}H-NMR ($CDCl_3$) δ 1.08 (3H, s), 1.52 (3H, s), 4.36 (2H, dd, *J*=15.8, 17.5), 4.85 (1H, d, *J*=7.9), 5.78 (1H, d, *J*=7.9), 7.20-7.56 (9H, m). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.54; H, 5.88; N, 4.13.

***N*-Propenoyl-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo [3.3.0]octane ((1*R*,5*S*)-III-29).** To a solution of (1*R*,5*S*)-**III-24** (371 mg, 1.83 mmol) in THF (10 mL) was added methylmagnesium bromide (2.0 mL, 1.9 mmol; 0.93 M ethereal solution) at –78 °C, and the mixture was stirred for 10 min at –78 °C. To this solution was added acryloyl chloride (0.22 mL, 2.7 mmol) at –78 °C, and the mixture was stirred at –78 °C for 10 min and then at 0 °C for 20 min. The reaction was quenched by adding saturated NH_4Cl aq. (5 mL). The mixture was extracted with ethyl acetate (3 × 10 mL). Usual workup gave a colorless solid, which was purified by column chromatography (hexane/ethyl acetate (9/1)) to give (1*R*,5*S*)-**III-29** (250 mg, 0.970 mmol, 53%) as colorless crystals, which was used in the following reaction without further purification: $[\alpha]^{20.8}_{589}$ +391 (*c* 4.45, $CHCl_3$).

***N*-(*E*-2-Butenoyl)-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane ((1*R*,5*S*)-III-30).** According to the procedure given for the

preparation of (1*R*,5*S*)-**III-29**, from (1*R*,5*S*)-**III-24** (271 mg, 1.33 mmol) and *E*-2-butenoyl chloride (0.27 g, 1.6 mmol), (1*R*,5*S*)-**III-30** (446 mg, 1.33 mmol, 100%) was obtained as a colorless solid. An analytical sample was recrystallized from hexane/benzene (19/1) to give colorless prisms: mp 157-158 °C; IR (KBr) 1760, 1685, 1635; ^{1}H-NMR ($CDCl_3$) 1.15 (3H, s), 1.58 (3H, s), 1.98 (3H, d, *J*=6.6), 4.90 (1H, d, *J*=7.9), 5.79 (1H, d, *J*=7.9), 7.1-7.5 (6H, m).

Diastereoselective Alkylation Reaction.

General Procedure. The diastereoselective alkylation reactions were performed on a 0.2-1.2 mmol scale. To a stirred 0.5 M solution of diisopropylamine (1.2 eq.) in THF was added butyllithium (1.1 eq.; 1.63 M solution in hexane) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Then, to this solution was added a 0.3-0.4 M solution of *N*-acyloxazolidinone (1*R*,5*S*)-**III-26** or (1*R*,5*S*)-**III-27** in THF at −78 °C, and the solution was stirred for 30 min at −78 °C. Finally, to this solution was added a 1 M solution of alkylhalide (3 to 6 eq.) in THF at −78 °C, and the reaction mixture was stirred at 0 °C for 0.5-3 h. The reaction was quenched by adding saturated NH_4Cl aq. (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). After the usual workup followed by removal of the highly polar by-products by short column chromatography (hexane/ethyl acetate (1/1)), HPLC analysis of the crude product mixture was performed in order to determine the diastereoselectivity, for which purpose an authentic sample was prepared by reaction of the lithium salt of racemic **9** with the corresponding racemic α-chiral carboxylic acid chloride. Purification by chromatography gave the corresponding α-alkylated carboximide **III-31a-d** as colorless crystals.

***N*-[(2*R*)-2-Methylbutanoyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-31a).** The reaction of the lithium enolate, derived from (1*R*,5*S*)-**III-26** (80.4 mg, 0.310 mmol), with ethyl iodide (0.30 g, 1.9 mmol) for 3 h at 0 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-31a** (62.6 mg, 0.179 mmol, 57%) as colorless crystals. The ratio of **III-31a** and its 2*S* isomer was determined to be >99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.44, longer retention time for the 2*R* isomer). An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]^{22.0}_{589}$ +296 (*c* 3.61, $CHCl_3$); mp 149.0-149.5 °C; IR (KBr) 1762,

1695; ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, t, *J*=7.5), 1.14 (3H, s), 1.19 (3H, d, *J*=6.7), 1.45 (1H, m), 1.56 (3H, s), 1.85 (1H, m), 3.70 (1H, m), 4.85 (1H, d, *J*=7.8), 5.77 (1H, d, *J*=7.8), 7.25-7.53 (4H, m). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.03; H, 7.44; N, 4.82.

***N*-[(2*R*)-2-Methylpent-4-enoyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-31b).** The reaction of the lithium enolate, derived from (1*R*,5*S*)-**III-26** (67.5 mg, 0.249 mmol), with allyl bromide (0.10 g, 0.83 mmol) for 1 h at 0 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-31b** (70.0 mg, 0.236 mmol, 95%) as colorless crystals. The ratio of **III-31b** and its 2*S* isomer was determined to be 99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.71, longer retention time for the 2*R* isomer). An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]^{22.0}_{589}$ +292 (*c* 3.78, $CHCl_3$); mp 85.0-85.5 °C; IR (KBr) 1762, 1695; ^{1}H-NMR ($CDCl_3$) δ 1.12 (3H, s), 1.20 (3H, d, *J*=6.7), 1.55 (3H, s), 2.15 (1H, m), 2.60 (1H, m), 3.88 (1H, m), 4.85 (1H, d, *J*=7.8), 5.07 (1H, d, *J*=19.3), 5.09 (1H, d, *J*=12.0), 5.77 (1H, d, *J*=7.8), 5.81(1H, m), 7.25-7.51 (4H, m). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.19; H, 7.10; N, 4.57.

***N*-[(2*R*)-2-Methyl-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-31c).** The reaction of the lithium enolate, derived from (1*R*,5*S*)-**III-26** (303 mg, 1.17 mmol), with benzyl bromide (0.60 g, 3.5 mmol) for 0.5 h at 0 °C, followed by purification by column chromatography (hexane/ethyl acetate (9/1)), gave **III-31c** (408 mg, 1.17 mmol, quant.) as colorless crystals. The ratio of **III-31c** and its 2*S* isomer was determined to be 99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.69, longer retention time for the 2*R* isomer). An analytical sample was recrystallized from petroleum ether to give colorless prisms: $[\alpha]^{22.0}_{589}$ +223 (*c* 2.24, $CHCl_3$); mp 108.5-109.0 °C; IR (KBr) 1770, 1690; ^{1}H-NMR ($CDCl_3$) δ 0.86 (3H, s), 1.18 (3H, d, *J*=6.8), 1.51 (3H, s), 2.60 (1H, dd, *J*=8.3, 13.0), 3.22 (1H, dd, *J*=6.2, 13.0), 4.18 (1H, m), 4.85 (1H, d, *J*=7.9), 5.77 (1H, d, *J*=7.9), 7.21-7.50 (9H, m). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.61; H, 6.69; N, 3.88.

***N*-[(2*S*)-2-Methyl-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-31d).** The reaction of the lithium enolate, derived from (1*R*,5*S*)-**III-27** (130 mg, 0.387 mmol), with methyl iodide (0.25 g, 1.8 mmol) for 1 h at 0 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-31d** (113 mg, 0.322 mmol, 83%) as colorless crystals. The ratio of **III-31d** and its 2*R* isomer was determined to be 97:3 by HPLC analysis (hexane/ethyl acetate (9/1), α 1.71, shorter retention time for the 2*S* isomer). An analytical sample was recrystallized from petroleum ether to give colorless needles: $[\alpha]^{22.8}_{589}$ +313 (*c* 5.63, $CHCl_3$); mp 111.0-111.5 °C; IR (KBr) 1770, 1690; ^{1}H-NMR ($CDCl_3$) δ 1.10 (3H, s), 1.28 (3H, d, *J*=7.0), 1.55 (3H, s), 2.74 (1H, dd, *J*=6.2, 13.5), 3.07 (1H, dd, *J*=6.2, 13.5), 4.20 (1H, m), 4.68 (1H, d, *J*=7.9), 5.56 (1H, d, *J*=7.9), 7.12-7.51 (9H, m). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.36; H, 6.67; N, 3.89.

Hydrolysis of III-31c with Lithium Hydroperoxide. To a solution of **III-31c** (349 mg, 1.00 mmol) in a mixture of THF (4 mL) and water (1 mL) was added 35% H_2O_2 aq. (0.4 mL, 4 mmol) and $LiOH{\cdot}H_2O$ (68.3 mg, 1.63 mmol) at 0 °C, and the reaction mixture was stirred for 2.5 h at 0 °C. Then, 1 M Na_2SO_3 aq. (3 mL) was added to the mixture. After the THF was evaporated, 1 M KOH aq. (10 mL) was added to the resulting residue, and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 extracts were washed with 1 M KOH aq. (10 mL). Usual workup of the CH_2Cl_2 layer gave oxazolidinone (1*R*,5*S*)-**III-24** (204 mg, 1.00 mmol, quant.). On the other hand, the aqueous layer was cooled to 0 °C, acidified to about pH 1 with 6 M HCl aq., and extracted with ethyl acetate (3 × 10 mL). Usual workup of the extracts gave (*R*)-2-methyl-3-phenylpropanoic acid (**III-32**) (156 mg, 0.950 mmol, 95 %): $[\alpha]^{19.2}_{589}$ –27.3 (*c* 7.66, $CHCl_3$) (lit. $[\alpha]_{589}$ –25.4 (neat) for the *R* isomer).[4] The enantiomeric purity of **III-32** was confirmed as follows: Treatment of **III-32** (150 mg, 0.911 mmol) with borane-THF complex (1.8 mL, 1.8 mmol: 1.0 M solution in THF) at rt for 1 h gave (*R*)-2-methyl-3-phenylpropanol (137 mg, 0.911 mmol, 100%), whose enantiomeric purity was determined to be >99% by ^{1}H-NMR analysis of the corresponding (+)-MTPA ester **III-33**.

Diastereoselective Acylation Reaction.

***N*-[(2*S*)-2-Methyl-3-oxobutanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-34a).** To a solution of diisopropylamine (105 mg, 1.03 mmol) in THF (1.5 mL) was added butyllithium (0.58 mL, 0.93 mmol; 1.60 M solution in hexane) at 0 °C, and the mixture was stirred for 30 min at 0 °C. To this solution was added a solution of (1*S*,5*R*)-**III-26** (214 mg, 0.824 mmol) in THF (1.5 mL) at −78 °C, and the solution was stirred for 30 min at −78 °C. Then the resulting solution of the lithium enolate in THF was added to a solution of acetyl chloride (0.15 g, 1.9 mmol) in THF (1.5 mL) via a cannular at −78 °C (cannulation time: 3 min). The reaction was immediately quenched by adding saturated NH_4Cl aq. (5 mL). Then the mixture was allowed to warm to rt and extracted with ether (3 × 15 mL). After usual workup of the extracts, the highly polar by-products were removed by short column chromatography (ether). The ratio of **16a** to its 2*R* isomer was determined to be 98:2 by HPLC analysis of the crude product mixture (hexane/ethyl acetate (5/1), α 1.86, longer retention time for the 2*S* isomer), for which purpose an authentic sample was prepared by epimerization of purified **III-34a** with a 1M solution of about 10 eq. triethylamine in dichloromethane for 12 h at room temperature. Purification by column chromatography (hexane/ether (4/1)) gave **III-34a** as colorless crystals (222 mg, 0.737 mmol, 89%). An analytical sample was recrystallized from petroleum ether/benzene (19/1) to give colorless prisms: $[\alpha]^{22.4}_{589}$ –218 (*c* 4.86, $CHCl_3$); mp 138.0-138.5 °C; IR (KBr) 1765, 1720, 1700; ^{1}H-NMR ($CDCl_3$) 1.25 (3H, s), 1.44 (3H, d, *J*=7.3), 1.59 (3H, s), 2.33 (3H, s), 4.55 (1H, q, *J*=7.33), 4.82 (1H, d, *J*=7.6), 5.79 (1H, d, *J*=7.6), 7.23-7.51 (4H, m). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.67; H, 6.37; N, 4.54.

***N*-[(2*S*)-2-Methyl-3-oxo-3-phenylpropionyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-34b).** A solution of the lithium enolate, derived from (1*S*,5*R*)-**III-26** (112 mg, 0.432 mmol), in THF (1.5 mL) was added to a solution of benzoyl chloride (0.10 g, 0.71 mmol) in THF (1.5 mL). The reaction was immediately quenched by adding saturated NH_4Cl aq. (5 mL). According to the procedure given for the preparation of **III-34a**, the ratio of the titled compound and its 2*R* isomer was determined to be >99:1 by HPLC analysis (hexane/ethyl acetate (4/1), α 2.49, longer retention

time for the 2*S* isomer). Purification of the crude products by column chromatography gave **III-34b** (146 mg, 0.400 mmol, 86%) as colorless crystals. An analytical sample was recrystallized from petroleum ether/benzene (19/1) to give colorless prisms: $[\alpha]^{22.4}_{589}$ –113 (*c* 1.29, $CHCl_3$); mp 152.5-153.0 °C; IR (KBr) 1770, 1710, 1685; ^{1}H-NMR ($CDCl_3$) 1.27 (3H, s), 1.51 (3H, d, *J*=7.3), 1.59 (3H, s), 4.87 (1H, d, *J*=7.9), 5.45 (1H, q, *J*=7.3), 5.81 (1H, d, *J*=7.9), 7.21-8.01 (9H, m). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.45; H, 5.88; N, 3.86.

***N*-[(2*S*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (*syn*-III-35).** To a solution of **III-34b** (129 mg, 0.356 mmol) in CH_2Cl_2 (20 mL) was added zinc borohydride (7.6 mL, 1.1 mmol; 0.14 M ethereal solution) at –78 °C, and the mixture was stirred for 1 h at 0 °C. After adding water (10 mL) to the mixture, filtration through celite pad was performed in order to remove the insoluble materials, and the filtrate was extracted with CH_2Cl_2 (3 × 10 mL). Usual workup of the extracts, followed by purification by PTLC ($CHCl_3$), gave *syn*-**III-35** (124 mg, 0.338 mmol, 95%) and its 2*S*,3*S* isomer, *anti*-**III-35** (4.6 mg, 3.5%). The relative stereochemistry of *anti*-**III-35** was established by a comparison of its ^{1}H-NMR spectrum with those of several kinds of known aldol adducts, obtained by the reactions of chiral *N*-propionyloxazolidinones with benzaldehyde.[16] An analytical sample of *syn*-**III-35** was recrystallized from hexane/benzene (19/1) to give colorless prisms: $[\alpha]^{22.0}_{589}$ –261 (*c* 1.07, $CHCl_3$); mp 135.5-136.0 °C; IR (KBr) 3425, 1780, 1762, 1695; ^{1}H-NMR ($CDCl_3$) 0.98 (3H, s), 1.17 (3H, d, *J*=6.9), 1.54 (3H, s), 2.83 (1H, d, *J*=3.0), 4.25 (1H, dq, *J*=3.3, 6.9), 4.86 (1H, d, *J*=7.6), 5.22 (1H, dd, *J*=3.0, 3.3), 5.80 (1H, d, *J*=7.6), 7.21-7.52 (9H, m). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.09; H, 6.41; N, 3.71.

Hydrolysis of *syn*-III-35 with Lithium Hydroperoxide. To a solution of *syn*-**III-35** (98.6 mg, 0.270 mmol) in a mixture of THF (1.2 mL) and water (0.3 mL) was added 35% H_2O_2 aq. (0.15 mL, 1.5 mmol) and $LiOH{\cdot}H_2O$ (23.0 mg, 0.55 mmol) at 0 °C. After the solution was stirred for 3 h at 0 °C, Na_2SO_3 (0.2 g) in water (1 mL) and 1 M HCl aq. (10 mL) were added in turn to the solution, and the resulting mixture was extracted with ethyl acetate (4 × 10 mL). Usual workup of the extracts gave the crude product mixture, which was treated

with excess CH_2N_2 in THF. After quenching the reaction by adding acetic acid, followed by concentration of the mixture under reduced pressure, the resulting crude product were purified by PTLC (hexane/ethyl acetate (2/1)) to give oxazolidinone (1*S*,5*R*)-**III-24** (51.3 mg, 0.252 mmol, 93%) and methyl (2*S*,3*R*)-3-hydroxy-2-methyl-3-phenylpropionate (**III-36**) (50.7 mg, 0.261 mmol, 97%): $[\alpha]^{22.0}_{589}$ –22.3 (*c* 2.31, $CHCl_3$) (lit. $[\alpha]^{25}_{589}$ –23.1 (c 3.2, $CHCl_3$) for the 2*S*,3*R* isomer).[5] The enantiomeric purity of **III-36** was confirmed to be >99% by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/2-propanol (15/1), α 1.12, shorter retention time for the 2*S*,3*R* isomer).

Diastereoselective Bromination.

***N*-[(2*S*)-2-Bromo-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-37).** To a solution of (1*R*,5*S*)-**III-27** (141 mg, 0.420 mmol) in CH_2Cl_2 (1.5 mL) were successively added dibutylboryl triflate (0.46 mL, 0.46 mmol; 1.0 M CH_2Cl_2 solution) and a solution of diisopropylethylamine (68.0 mg, 0.526 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C, and the resulting solution was stirred at 0 °C for 1 h. Then the solution of the boron enolate in CH_2Cl_2 was added to a suspension of NBS (0.90 g, 0.51 mmol) in CH_2Cl_2 (1 mL) via a cannular at –78 °C (cannulation time: 3 min), and the resulting mixture was stirred for 1.5 h at –78 °C. The reaction was quenched by adding 0.5 M $NaHSO_4$ (5 mL) at –78 °C, and the mixture was allowed to warm to rt and then extracted with ether (3 × 10 mL). After usual workup of the extracts, the highly polar by-products were removed by short column chromatography (ether). The ratio of **III-37** to its 2*R* isomer was determined to be 99:1 by HPLC analysis (hexane/ethyl acetate (9/1), α 2.71, longer retention time for the 2*S* isomer), for which purpose an authentic sample was prepared by epimerization of purified **III-37** with lithium bromide in refluxing THF. Purification by column chromatography (hexane/ether (9/1)) gave **III-37** (165 mg, 0.398 mmol, 95%) as a colorless solid mass: $[\alpha]^{22.8}_{589}$ +200 (*c* 3.11, $CHCl_3$); mp 63.0-64.5 °C; IR (KBr) 1770, 1705, 510; ^{1}H-NMR ($CDCl_3$) 1.24 (3H, s), 1.57 (3H, s), 3.34 (1H, dd, *J*=6.6, 13.9), 3.59 (1H, dd, *J*=8.9, 13.9), 4.75 (1H, d, *J*=7.7), 5.66 (1H, d, *J*=7.7), 5.95 (1H, dd, *J*=6.6, 8.9), 7.21-7.50 (9H, m); HRMS(EI) calcd for $C_{21}H_{20}BrNO_3$ 415.0606, found 415.0620.

***N*-[(2*R*)-2-Azido-3-phenylpropionyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-38).** To a solution of diastereomerically pure **III-37** (120 mg, 0.290 mmol) in CH_2Cl_2 (2 mL) was added 1,1,3,3-tetramethylguanidinium azide (0.23 g, 1.5 mmol) in one portion at 0 °C, and the solution was stirred for 1 h at 0 °C. After adding saturated aqueous $NaHCO_3$ (5 mL), the mixture was extracted with ether (3 × 10 mL). Usual workup of the extracts gave a pale yellow viscous oil, which was purified by PTLC (hexane/ethyl acetate (5/1)) to give pure **III-38** (105 mg, 0.279 mmol, 96%) as colorless crystals. An analytical sample was recrystallized from hexane/benzene (19/1) to give colorless prisms: $[\alpha]^{22.4}_{589}$ +292 (*c* 1.08, $CHCl_3$); mp 109.0-109.5 °C; IR (KBr) 2120, 1765, 1700, 1360, 1200; ^{1}H-NMR ($CDCl_3$) 1.06 (3H, s), 1.58 (3H, s), 2.97 (1H, dd, *J*=10.2, 13.5), 3.37 (1H, dd, *J*=4.0, 13.5), 4.91 (1H, d, *J*=7.7), 5.26 (1H, dd, *J*=4.0, 10.2), 5.90 (1H, d, *J*=7.7), 7.21-7.56 (9H, m). Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 67.09; H, 5.54; N, 14.71.

Hydrolysis of III-38 with Lithium Hydroxide. To a solution of **III-38** (105 mg, 0.279 mmol) in THF (2 mL) was added a solution of $LiOH{\cdot}H_2O$ (50 mg) in water (4 mL) at 0 °C and the mixture was stirred for 2 h at 0 °C. After adding 1 M KOH aq. (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). Usual workup of the combined extracts gave oxazolidinone (1*R*,5*S*)-**III-24** (0.287 mmol, quant.). On the other hand, the aqueous layer was cooled to 0 °C, acidified to pH 1 with 6 M HCl aq., and extracted with ether (4 × 10 mL). Usual workup of the combined extracts gave (*R*)-2-azido-3-phenylpropionic acid (**III-39**) (47.6 mg, 0.249, 89%): $[\alpha]^{21.6}_{589}$ +66.2 (*c* 2.00, $CHCl_3$) (lit. $[\alpha]^{21.6}_{589}$ +68.6 (*c* 1.40, $CHCl_3$) for the *R* isomer).[5] The enantiomeric purity of **III-39** was determined as follows: A solution of α-azido acid **III-39** (37.0 mg, 0.194 mmol) in a mixture of acetic acid (3 mL) and water (1 mL) was treated with 5% Pd/C (30 mg) under a H_2 atmosphere for 7 h. Then the reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to give a colorless solid. To a suspension of the product in methanol (5 mL) was added thionyl chloride (1 mL) drop by drop at 0 °C, and the reaction mixture was refluxed for 2 h. The volatiles were removed under reduced pressure to yield crude methyl (*R*)-phenylalaninate hydrochloride as a slightly brown solid. A suspension of this crude product in CH_2Cl_2 (4 mL) was treated with triethylamine (0.5 mL) and (+)-MTPA chloride (0.10 g, 0.40

mmol), and the mixture was stirred for 2 h at rt. Concentration of the mixture under reduced pressure, followed by purification by PTLC (hexane/ethyl acetate (9/1)), gave the corresponding *N*-(+)-MTPA amino acid methyl ester **III-10**, whose diastereomeric purity was determined to be >99% by ^{1}H-NMR analysis.

Diasteroselective Hydroxylation.

***N*-[(2*R*)-2-Hydroxy-2-phenylacetyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane III-41.** To sodium hexamethyldisilazide (1.2 mL, 0.6 mmol; 0.5 M THF solution) was added a solution of (1*S*,5*R*)-**III-28** (155 mg, 0.482 mmol) in THF (1.2 mL) at –78 °C, and the resulting solution was stirred for 0.5 h at –78 °C. Then, to the solution was added a solution of 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine (0.20 g, 0.73 mmol) in THF (1.5 mL) drop by drop over a period of 5 min at –78 °C, and the reaction mixture was stirred for 10 min at –78 °C. The reaction was quenched by adding a solution of camphorsulfonic acid (0.56 g, 2.4 mmol) in THF (5.0 mL). The mixture was allowed to warm to rt and then passed through a short silica gel pad (eluent: CH_2Cl_2). Evaporation of the filtrate, followed by purification by PTLC (hexane/ethyl acetate (1/1)), gave 137 mg (0.406 mmol, 84%) of a mixture of **III-41** and its 2*S* isomer as an oil. The diastereomer ratio was determined to be 93:7 by ^{1}H-NMR analysis of the diastereomeric mixture. Removal of the isomeric impurity could be performed by recrystallization of the product from petroleum ether/CH_2Cl_2 (2/1) to give colorless needles: $[\alpha]^{22.4}_{589}$ –361 (*c* 1.00, $CHCl_3$); mp 124.0-125.0 °C; IR (KBr) 3450, 1780, 1700; ^{1}H-NMR ($CDCl_3$) 1.19 (3H, s), 1.61 (3H, s), 4.08 (1H, d, *J*=8.3), 4.73 (1H, d, *J*=7.6), 5.66 (1H, d, *J*=7.6), 6.28 (1H, d, *J*=8.3), 7.21-7.50 (9H, m). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.08; H, 5.64; N, 4.13.

Methanolysis of III-41 with Magnesium Methoxide. A mixture of **III-41** and its 2*S* isomer (56.5 mg, 0.167 mmol, 2*R*:2*S*=93:7) was treated with magnesium methoxide (7.5 mL, 0.83 mmol; 0.11 M solution in methanol) at 0 °C, and the mixture was stirred for 0.5 h at 0 °C. The reaction was quenched by adding saturated NH_4Cl aq. (10 mL). The resulting mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Usual workup of the extracts, followed by purification by PTLC (hexane/ethyl acetate (2/1)), gave

(1*S*,5*R*)-**III-24** (30.0 mg, 0.148 mmol, 88%) and methyl mandelate (**III-42**) (25.4 mg, 0.153 mmol, 92%). The enantiomer ratio for **III-42** was determined to be *R*:*S*=93:7 by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/2-propanol (9/1), α 1.33, longer retention time for the *R* isomer), for which purpose authentic samples of methyl (*R*)- and (*S*)-mandelate were prepared by treatment of respectively commercially available (*R*)- and (*S*)-mandelic acid with excess CH_2N_2.

Diasteroselective Aldol Reaction.

Procedure A. The reactions were performed on a 0.4-0.6 mmol scale. To a solution of (1*S*,5*R*)-**III-25** in CH_2Cl_2 were successively added $TiCl_4$ (1.1 eq.; 1.0 M solution in CH_2Cl_2) and a 1.0 M solution of diisopropylethylamine (1.2 eq.) in CH_2Cl_2 at –78 °C, and the resulting solution was stirred at 0 °C for 1 h. Then, to this solution was added a 2.5 M solution of aldehyde (3 eq.) in CH_2Cl_2 at -78 °C, and the solution was stirred for 30 min at -78 °C. The resulting mixture was stirred for 3 h at -78 °C. The reaction was quenched by adding saturated $NaHSO_4$ aq. (5 mL) at -78 °C, and the mixture was allowed to warm to rt and then extracted with CH_2Cl_2 (4 × 10 mL). After the usual workup followed by removal of the highly polar by-products by short column chromatography (hexane/ethyl acetate (1/1)), HPLC analysis of the crude product mixture was performed in order to determine the diastereoselectivity. Purification by PTLC (hexane:ethyl acetate:CH_2Cl_2=3:1:1) gave the corresponding aldol adduct as colorless crystals.

Procedure B. The reactions were performed on a 0.4-0.6 mmol scale. To a stirred 0.6 M ethereal solution of diisopropylamine (1.3 eq.) was added butyllithium (1.1 eq.; 1.6 M solution in hexane) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Then, to this solution was added a 0.2 M ethereal solution of (1*S*,5*R*)-**III-25** at -78 °C, and the solution was stirred for 30 min at -78 °C. Then, to the resulting suspension was added $TiCl_2(i\text{-PrO})_2$ (3.5 eq.; 1.13 M solution in toluene) at -78 °C, and the solution was stirred for 2 h at -40 °C. Finally, to this solution was added a 1.4 M ethereal solution of aldehyde (3.0 eq.), and the reaction mixture was stirred at -78 °C for 2.0 h. The reaction was quenched by adding saturated NH_4Cl aq. (5 mL), and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The

workup, determination of the diastereoselectivity, and purification of the products were similarly performed as described in Procedure A.

Procedure C. The reactions were performed on a 0.4-0.6 mmol scale. To a stirred 0.5 M ethereal solution of diisopropylamine (1.3 eq.) was added butyllithium (1.1 eq.; 1.6 M solution in hexane) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Then, to this solution was added a 0.16 M ethereal solution of N-acyloxazolidinone (1*S*,5*R*)-**III-25** at -78 °C, and the solution was stirred for 30 min at -78 °C. To the resulting suspension was added a 1.2 M ethereal solution of aldehyde (3.0 eq.), and the reaction mixture was stirred at -78 °C for 3 h. The reaction was quenched by adding saturated NH_4Cl aq. (5 mL), and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The workup, determination of the diastereoselectivity, and purification of the products were similarly performed as described in Procedure A.

***N*-[(3*S*)-3-Hydroxynonanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-51a).** The reaction of the titanium enolate with heptanal, derived from (1*S*,5*R*)-**III-25** (95.1 mg, 0.388 mmol), according to the procedure A, gave 94.3 mg (0.262 mmol, 68 %) of a mixture of **III-51a** and **III-52a**. The diastereomeric ratio (**III-51a**:**III-52a**) was determined to be 74:26 by HPLC analysis (hexane/ethyl acetate (3/1)). Further purification by PTLC gave diastereomerically pure **III-51a** as a colorless solid: mp 71-77 °C; $[\alpha]^{22.8}_{589}$ –218 (c 1.47, $CHCl_3$); IR (KBr) 1775, 1675; ^{1}H-NMR ($CDCl_3$) δ 0.88(3H, t, *J*=6.9), 1.15 (3H, s), 1.42 (10H, m), 1.57 (3H, s), 3.10 (1H, dd, *J*=7.9, 17.3), 3.18 (1H, dd, *J*=4.0, 17.5), 4.06-4.15 (1H, m), 4.87 (1H, d, *J*=7.9), 5.80 (1H, d, J=7.9), 7.25-7.54 (4H, m).

***N*-[(3*R*)-3-Hydroxynonanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-52a).** Obtained as a colorless solid: mp 79-84 °C; $[\alpha]^{22.8}_{589}$ –271 (c 0.96, $CHCl_3$); IR (KBr) 1775, 1690; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J*=6.9), 1.15 (3H, s), 1.29-1.54 (10H, m), 1.57 (3H, s), 2.89 (1H, d, *J*=4.0), 3.02 (1H, dd, *J*=9.2, 17.5), 3.25 (1H, dd, *J*=2.3, 17.7), 4.08-4.18 (1H, m), 4.85 (1H, d, *J*=7.9), 5.80 (1H, d, *J*=7.9), 7.25-7.52 (4H, m).

***N*-[(3S)-3-Hydroxy-4-methylpentanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-51b).** The reaction of the titanium enolate

with isobutyraldehyde, derived from (1*S*,5*R*)-**III-25** (99.9 mg, 0.407 mmol), according to the procedure A, gave 73.8 mg (0.233 mmol, 57 %) of a mixture of **III-51b** and **III-52b**. The diastereomeric ratio (**III-51b**:**III-52b**) was determined to be 88:12 by HPLC analysis (hexane/ethyl acetate (3/1)). Further purification by PTLC gave diastereomerically pure **III-51b** as a colorless solid: mp 67-72 °C; $[\alpha]^{22.8}_{589}$ –253 (c 2.19, $CHCl_3$); IR (KBr) 1775, 1680; ^{1}H-NMR ($CDCl_3$) δ 0.97 (3H, d, *J*=6.3), 1.00 (3H, d, *J*=6.6), 1.16 (3H, s), 1.57 (3H, s), 1.73-1.85 (1H, m), 3.06 (2H, dd, *J*=4.9, 44.7), 3.15 (1H, d, *J*=7.9), 3.84-3.92 (1H, m), 4.86 (1H, d, *J*=7.9), 5.80 (1H, d, *J*=7.9), 7.28-7.55 (4H, m).

***N*-[(3*R*)-3-Hydroxy-4-methylpentanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-52b).** Obtained as a colorless solid: mp 92-95 °C; $[\alpha]^{22.8}_{589}$ –261 (c 0.17, $CHCl_3$); IR (KBr) 1780, 1680; ^{1}H-NMR ($CDCl_3$) δ 0.98 (3H, d, *J*=3.6), 1.00 (3H, d, *J*=3.6), 1.15 (3H, s), 1.57 (3H, s), 1.79 (1H, m), 2.79 (1H, d, *J*=4.3), 3.05 (1H, dd, *J*=9.9, 17.2), 3.23 (1H, dd, *J*=2.6, 17.2), 3.89-3.97 (1H, m), 4.86 (1H, d, *J*=7.6), 5.86 (1H, d, *J*=7.5), 7.23-7.53 (4H, m).

***N*-[(3*R*)-3-Hydroxy-4,4-dimethylpentanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-52c).**

The reaction of the titanium enolate derived from (1*S*,5*R*)-**III-25** (110.2 mg, 0.449 mmol), with pivalaldehyde, according to the procedure B, gave 134.3 mg of a mixture of **III-51c**, **III-52c,** and (1*S*,5*R*)-**III-25**. ^{1}H-NMR analysis of this mixture revealed the combined yield of the aldol adducts was 79%. The diastereomeric ratio (**III-51c**:**III-52c**) was determined to be 88:12 by HPLC analysis (hexane:ethyl acetate=3:1). Further purification by PTLC gave diastereomerically pure **III-52c** as a colorless solid: mp 84-90 °C; $[\alpha]^{22.8}_{589}$ –237 (c 0.49, $CHCl_3$); IR (KBr) 1775, 1695; ^{1}H-NMR ($CDCl_3$) δ 0.97 (9H, s), 1.15 (3H, s), 1.57 (3H, s), 2.72 (1H, d, *J*=4.6), 3.03 (1H, dd, *J*=10.9, 17.0), 3.24 (1H, dd, *J*=2.0, 16.8), 3.82-3.87 (1H, m), 4.86 (1H, d, *J*=7.6), 5.79 (1H, d, *J*=7.9), 7.24-7.53 (4H, m).

***N*-[(3*S*)-3-Hydroxy-4,4-dimethylpentanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-51c).** Not separable from (1*S*,5*R*)-**III-25**. ^{1}H-NMR ($CDCl_3$) δ 0.97 (9H, s), 1.16 (3H, s), 1.57 (3H, s), 2.94 (1H, d, *J*=5.6), 2.96-3.29 (2H, m), 3.76-3.82 (1H, m), 4.86 (1H, d, *J*=7.9), 7.80 (1H, d, *J*=7.6), 7.24-7.53 (4H, m).

***N*-[(3*S*)-3-Hydroxy-3-phenylpropanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-51d).** The reaction of the lithium enolate derived from (1*S*,5*R*)-**III-25** (96.2 mg, 0.392 mmol), with benzaldehyde, according to the procedure C, gave 130.6 mg (0.372 mmol, 95 %) of a mixture of **III-51d** and **III-52d**. The diastereomeric ratio (**III-51d**:**III-52d**) was determined to be 88:12 by HPLC analysis (hexane/ethyl acetate (3/1)). Further purification by PTLC gave diastereomerically pure **III-51d** as a colorless solid: mp 126-131 °C; $[\alpha]^{22.8}_{589}$ –225 (c 3.33, $CHCl_3$); IR (KBr) 1780, 1680; ^{1}H-NMR ($CDCl_3$) δ 1.12 (3H, s), 1.57 (3H, s), 3.36 (1H, dd, *J*=3.0, 17.5), 3.44 (1H, d, *J*=4.6), 3.54 (1H, dd, *J*=9.6, 17.2), 4.87 (1H, d, *J*=7.9), 5.12-5.27 (1H, m), 5.80 (1H, d, *J*=7.6), 7.24-7.51 (9H, m).

***N*-[(3*R*)-3-Hydroxy-3-phenylpropanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-52d).** Obtained as a colorless solid: mp 123-131 °C; $[\alpha]^{22.8}_{589}$ –262 (c 0.58, $CHCl_3$); IR (KBr) 1790, 1680; ^{1}H-NMR (CDCl3) δ 1.15 (3H, s), 1.58 (3H, s), 3.20 (1H, s), 3.44 (1H, d, *J*=7.3), 3.44 (1H, d, *J*=5.3), 4.87 (1H, d, *J*=7.9), 5.24-5.33 (1H, m), 5.80 (1H, d, *J*=7.9), 7.26-7.51 (9H, m).

Hydrolysis of III-51b with Lithium Hydroperoxide. To a solution of **III-51b** (386 mg, 1.21 mmol) in a mixture of THF (4 mL) and water (1 mL) was added 35% H_2O_2 aq. (0.5 mL, 5 mmol) and LiOH·H_2O (0.10 g, 2.4 mmol) at 0 °C, and the reaction mixture was stirred for 2.5 h at 0 °C. Then, 1 M Na_2SO_3 aq. (3 mL) was added to the mixture. After the THF was evaporated, 1 M KOH aq. (10 mL) was added to the resulting residue, and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 extracts were washed with 1 M KOH aq. (10 mL). Usual workup of the CH_2Cl_2 layer gave oxazolidinone (1*S*,5*R*)-**III-24** (246 mg, 1.21 mmol, quant.). On the other hand, the aqueous layer was cooled to 0 °C, acidified to about pH 1 with 6 M HCl aq., and extracted with ether (3 × 10 mL). Usual workup of the extracts gave (+)$_{589}$-(*R*)-3-hydroxy-4-methylpentanoic acid (**III-56**) (144 mg, 1.09 mmol, 90 %): $[\alpha]^{24.4}_{589}$ +40.3 (*c* 1.12, $CHCl_3$) (lit. $[\alpha]^{25}_{589}$ +39.9 (*c* 2.84, $CHCl_3$) for the *R* isomer).[6c]

The Diastereoselective Diels-Alder Reaction

Gereral Procedure. The diastereoselective Diels-Alder reactions were performed on a 0.2-0.7 mmol scale. To a stirred 0.5 M solution of **III-29** or **III-30** and diene (30 eq.) in CH_2Cl_2 (2.0 mL) was added Et_2AlCl (1.4 eq.; 0.86 M solution in hexane) at –78 °C. After the mixture was stirred at –78 °C (in some cases, the reaction temperature was allowed to raise to –20 °C or 0 °C). The reaction was quenched by adding saturated aqueous ammonium chloride (5 mL), and the mixture was extracted with ether (3 × 10 mL). After usual workup and successive removal of the highly polar by-products by short column chromatography (hexane/ethyl acetate (1/1)), HPLC analysis of the crude mixture was performed in order to determine the diastereoselectivity, for which an authentic sample was prepared by the reaction of the lithium salt of racemic **III-24** with the corresponding racemic carboxylic acid chloride. Purification by PTLC or column chromatography (hexane/ethyl acetate (9/1)) gave the corresponding cycloadduct **III-61**–**III-67** as colorless crystals.

***N*-[(3*R*,4*R*,6*R*)-Bicyclo[2.2.1]heptene-4-carbonyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-61).** The reaction of (1*R*,5*S*)-**III-29** (89.0 mg, 0.346 mmol), with cyclopentadiene for 0.5 h at –78 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-61** (83.7 mg, 0.259 mmol, 75%) as a mixture with its diastereomers. The *endo*:*exo* ratio and the ratio of **III-61** and its (3*S*,4*S*,6*S*)-isomer were determined to be 97:3 and 98:2 by HPLC analysis (hexane/ethyl acetate (9/1)), respectively. An analytical sample was recrystallized from hexane to give colorless prisms: $[\alpha]^{22.8}_{589}$ +393 (c 4.19, $CHCl_3$); mp 144-145 °C; IR (KBr) 1790, 1700; ^{1}H-NMR (CDCl3) δ 1.14 (3H, s), 1.4-1.6 (3H, m), 1.52 (3H, s), 1.95 (1H, m), 2.97 (1H, br s), 3.42 (1H, br s), 4.05 (1H, m), 4.80 (1H, d, *J*=7.9), 5.76 (1H, d, *J*=7.9), 5.91 (1H, dd, *J*=3.0, 5.6), 6.32 (1H, dd, *J*=3.3, 5.6), 7.2-7.5 (4H, m).

***N*-[(3*R*,4*R*,5*S*,6*S*)-5-Methylbicyclo[2.2.1]heptene-4-carbonyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-62).** The reaction of (1*R*,5*S*)-**III-30** (198 mg, 0.731 mmol), with cyclopentadiene for 0.5 h at –78 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-62** (239 mg, 0.707 mmol, 97%) as a mixture with its diastereomers. The *endo*:*exo* ratio and the ratio of **III-62** and its (3*S*,4*S*,5*R*,6*R*)-isomer were determined to be 99:1 and >99:1 by HPLC analysis

(hexane/ethyl acetate (9/1)), respectively. An analytical sample was recrystallized from hexane to give colorless prisms: $[\alpha]^{22.8}_{589}$ +429 (c 4.77, $CHCl_3$); mp 105-106 °C; IR (KBr) 1770, 1697; ^{1}H-NMR ($CDCl_3$) δ 1.12 (3H, s), 1.15 (3H, d, *J*=7.3), 1.50 (1H, d, *J*=8.6), 1.51 (3H, s), 1.74 (1H, d, *J*=8.6), 2.10 (1H, m), 2.55 (1H, br s), 3.39 (1H, br s), 3.59 (1H, dd, *J*=3.3, 4.6), 4.82 (1H, d, *J*=7.9), 5.78 (1H, d, *J*=7.9), 5.81 (1H, dd, *J*=2.8, 5.8), 6.43 (1H, dd, *J*=3.0, 5.8), 7.2-7.5 (4H, m).

***N*-[(3*R*,4*R*,6*R*)-Bicyclo[2.2.2]octene-4-carbonyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-63).** The reaction of (1*R*,5*S*)-**III-29** (88.0 mg, 0.342 mmol), with cyclohexadiene for 1 h at –78 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-63** (51.1 mg, 0.151 mmol, 44%) as a mixture with its diastereomers. The *endo*:*exo* ratio and the ratio of **III-63** and its (3*S*,4*S*,5*S*)-isomer were determined to be 99:1 and 99:1 by HPLC analysis (hexane/ethyl acetate (9/1)), respectively. An analytical sample was recrystallized from hexane to give colorless prisms: mp 133-134 °C; IR (KBr) 1780, 1700; ^{1}H-NMR ($CDCl_3$) δ 1.14 (3H, s), 1.2-1.4 (2H, m), 1.5-1.6 (1H, m), 1.53 (3H, s), 1.7-1.9 (3H, m), 2.66 (1H, br s), 2.92 (1H, br s), 3.84 (1H, dt, *J*=2.0, 7.6), 4.81 (1H, d, *J*=7.9), 5.76 (1H, d, *J*=7.9), 6.10 (1H, t, *J*=7.4), 6.40 (1H, t, *J*=7.4), 7.2-7.5 (4H, m).

***N*-[(3*R*,4*R*,5*S*,6*S*)-5-Methylbicyclo[2.2.2]octene-4-carbonyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-64).** The reaction of (1*R*,5*S*)-**III-30** (104 mg, 0.382 mmol), with cyclohexadiene for 0.5 h at –78 °C and 0 °C for 1 h, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-64** (78.2 mg, 0.223 mmol, 58%) as a mixture with its diastereomers. The *endo*:*exo* ratio and the ratio of **III-64** and its (3*S*,4*S*,5*R*,6*R*)-isomer were determined to be 98:2 and 96:4 by HPLC analysis (hexane/ethyl acetate (9/1)), respectively. An analytical sample was recrystallized from hexane to give colorless prisms: mp 160-161 °C; IR (KBr) 1770, 1700; ^{1}H-NMR ($CDCl_3$) δ 1.04 (3H, d, *J*=6.9), 1.13 (3H, s), 1.2-1.4 (1H, m), 1.52 (3H, s), 1.5-1.6 (1H, m), 1.7-1.9 (2H, m), 2.25 (1H, quint, *J*=6.9), 2.36 (1H, br s), 2.84 (1H, br s), 3.29 (1H, d, *J*=6.3), 4.86 (1H, d, *J*=7.9), 5.78 (1H, d, *J*=7.9), 5.95 (1H, dd, *J*=6.9, 7.6), 6.58 (1H, dd, *J*=6.9, 8.3), 7.2-7.5 (4H, m).

***N*-[(1*R*)-4-Methyl-3-cyclohexenecarbonyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-65).** The reaction of (1*R*,5*S*)-**III-29** (54.5 mg, 0.211 mmol), with isoprene for 0.5 h at –78 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-65** (52.4 mg, 0.161 mmol, 76%) as a mixture with its diastereomer. The ratio of **III-65** and its (1*S*)-isomer was determined to be >99:1 by HPLC analysis (hexane/ethyl acetate (9/1)). An analytical sample was recrystallized from hexane to give colorless prisms: $[\alpha]^{22.8}_{589}$ +299 (c 2.58, $CHCl_3$); IR (KBr) 1780, 1700; ^{1}H-NMR ($CDCl_3$) δ 1.12 (3H, s), 1.55 (3H, s), 1.67 (3H, s), 1.7-2.4 (6H, m), 3.7-3.8 (1H, m), 4.87 (1H, d, *J*=7.9), 5.40 (1H, br d), 5.78 (1H, d, *J*=7.9), 7.2-7.5 (4H, m).

***N*-[(1*S*,2*S*)-2,4-Dimethyl-4-cyclohexenecarbonyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-66).** The reaction of (1*R*,5*S*)-**III-30** (196 mg, 0.724 mmol), with isoprene for 0.5 h at –78 °C and 1.5 h at 0 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-66** (160 mg, 0.471 mmol, 65%) as a mixture with its diastereomer. The ratio of **III-66** and its (1*R*,2*R*)-isomer was determined to be >99:1 by HPLC analysis (hexane/ethyl acetate (9/1)). An analytical sample was recrystallized from hexane to give colorless prisms: $[\alpha]^{22.8}_{589}$ +307 (c 3.10, $CHCl_3$); IR (KBr) 1775, 1690; ^{1}H-NMR ($CDCl_3$) δ 0.99 (3H, d, *J*=5.9), 1.12 (3H, s), 1.57 (3H, s), 1.65 (3H, s), 1.7-2.5 (5H, m), 3.67 (1H, ddd, *J*=5.3, 10.5, 10.6), 4.88 (1H, d, *J*=7.9), 5.37 (1H, br s), 5.78 (1H, d, *J*=7.9), 7.2-7.5 (4H, m).

***N*-[(1*R*)-3,4-Dimethyl-3-cyclohexenecarbonyl]-(1*R*,5*S*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-67).** The reaction of (1*R*,5*S*)-**III-29** (136 mg, 0.527 mmol), with isoprene for 0.5 h at –78 °C and 1 h at –20 °C, followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-67** (59.6 mg, 0.176 mmol, 33%) as a mixture with its diastereomer. The ratio of **III-67** and its (1*S*)-isomer was determined to be 98:2 by HPLC analysis (hexane/ethyl acetate (9/1)). An analytical sample was recrystallized from hexane to give colorless prisms: IR (KBr) 1780, 1700; ^{1}H-NMR ($CDCl_3$) δ 1.13 (3H, s), 1.56 (3H, s), 1.62 (6H, s), 1.6-2.3 (6H, m), 3.7-3.9 (1H, m), 4.87 (1H, d, *J*=7.9), 5.78 (1H, d, *J*=7.9), 7.2-7.5 (4H, m).

Conversion of III-62 to its Corresponding Benzyl ester. A solution of benzylalcohol (81.8 mg, 0.756 mmol) in THF (2 mL) was added butyllithium (0.37 mL, 0.60

mmol; 1.63 M solution in hexane) at –78 °C, and the mixture was stirred for 10 min at –78 °C. To this solution was added a solution of **III-62** (99.2 mg, 0.294 mmol) in THF (2 mL) at –78 °C, and the mixture was stirred at 0 °C for 3 h. The reaction was quenched by adding saturated NH_4Cl aq. (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). Usual workup of the extracts, followed by purification by PTLC (hexane/ethyl acetate (2/1)), gave (1*R*,5*S*)-**III-24** (56.6 mg, 0.278 mmol, 95%) and phenylmethyl (+)$_{589}$-(3*R*,4*R*,5*S*,6*S*)-5-methylbicyclo[2.2.1]heptene-4-carboxylate (**III-68**) (66.6 mg, 0.275 mmol, 93%):: $[\alpha]^{22.4}_{589}$ –127 (*c* 3.30, $CHCl_3$) (lit. $[\alpha]_{589}$ –130 (c 2.08, $CHCl_3$)).[15a]

Details for X-ray structural analysis of *N*-[(2*S*)-2-Methyl-3-oxobutanoyl]-(1*S*,5*R*)-7,8-benzo-6,6-dimethyl-3-oxo-4-aza-2-oxabicyclo[3.3.0]octane (III-34a).

Chemical Formula	$C_{17}H_{19}NO_4$
Formula Weight	301.00
Crystal Size	0.70 × 0.40 × 0.030
a/Å	15.080 (2)
b/Å	9.126 (2)
c/Å	12.588 (1)
β/degree	112.730 (8)
Volume of Unit Cell	1597.9 (3)
Crystal System	Monoclinic
Space Group	$P2_1$
Z value	4
D_{calc}/g cm^{-3}	1.25
Reflections used	2711
R;Rw	0.0564; 0.0638
Goodness of Fit	1.62
Maximum Shift/e. s. d. in final cycle	0.0330

Maximum Negative Peak in Final Diff. Map/e Å^{-3}	–0.26
Maximum Positive Peak in Final Diff. Map/e Å^{-3}	0.22

Fractional Atomic Coordinates & U(iso)

atom	x/a	y/b	z/c	U(iso)
O 1	0.0844 (3)	-0.1920	0.4957 (3)	0.044
O 2	0.0837 (3)	-0.3742 (6)	0.3774 (4)	0.051
N 3	0.0055 (3)	-0.1527 (7)	0.3069 (4)	0.037
O 4	-0.0996 (3)	-0.0846 (7)	0.1347 (3)	0.057
O 5	0.3779 (4)	0.2331 (7)	0.3902 (4)	0.071
O 6	0.5602 (4)	0.1456 (7)	0.1923 (4)	0.079
O 7	0.3541 (4)	0.4036 (7)	0.2515 (5)	0.094
C 8	0.1099 (4)	0.0698 (8)	0.5417 (5)	0.041
C 9	-0.0039 (4)	-0.0121 (8)	0.3576 (4)	0.037
N 10	0.4572 (4)	0.2040 (7)	0.2746 (4)	0.049
C 11	0.0387 (4)	-0.0482 (8)	0.4874 (5)	0.042
C 12	-0.0485 (4)	-0.1800 (9)	0.1904 (5)	0.046
C 13	0.1161 (4)	0.1655 (8)	0.4599 (5)	0.042
C 14	0.0545 (4)	0.1194 (8)	0.3370 (5)	0.043
C 15	0.0602 (4)	-0.2526 (8)	0.3907 (5)	0.043
C 16	0.3791 (4)	-0.1238 (9)	0.3648 (6)	0.048
O 17	0.0821 (5)	-0.2133 (8)	0.0915 (6)	0.108
C 18	0.4204 (4)	-0.0709 (8)	0.2789 (5)	0.046
O 19	0.3630 (5)	0.2592 (8)	-0.0099 (5)	0.094
C 20	0.4779 (4)	0.0690 (8)	0.3419 (5)	0.045
C 21	0.1758 (4)	0.2876 (9)	0.4928 (6)	0.055
C 22	0.3898 (4)	-0.0229 (9)	0.4509 (5)	0.049
C 23	0.1221 (5)	0.0727 (9)	0.2765 (6)	0.061
C 24	0.3930 (6)	0.2940 (10)	0.3002 (7)	0.069
C25	0.4429 (4)	0.1076 (9)	0.4387 (5)	0.054
C26	0.1634 (4)	0.0913 (9)	0.6588 (5)	0.054
C27	0.0536 (5)	-0.3258 (9)	0.1165 (6)	0.059
C28	0.5056 (5)	0.2358 (10)	0.2021 (5)	0.060
C29	-0.0369 (4)	-0.3286 (8)	0.1422 (5)	0.049
C30	0.2295 (5)	0.3103 (10)	0.6108 (7)	0.067
C31	0.4857 (5)	0.3830 (9)	0.1412 (6)	0.062

C32	0.3386 (5)	-0. 351 (9)	0.1636 (6)	0.058
C33	0.3561 (5)	-0.0505 (11)	0.5378 (6)	0.066
C34	0.2237 (5)	0.2129 (10)	0.6931 (6)	0.062
C35	0.3340 (5)	-0.2582 (9)	0.3638 (7)	0.062
C36	-0.1234 (5)	-0.3589 (11)	0.0308 (6)	0.071
C37	0.3919 (6)	0.3754 (10)	0.0369 (6)	0.071
C38	-0.0137 (5)	0.2406 (9)	0.2701 (6)	0.058
C39	0.1014 (6(	-0.4698 (11)	0.1194 (8)	0.083
C40	0.4900 (5)	-0.1823 (10)	0.2629 (7)	0.072
C41	0.3114 (5)	-0.1831 (12)	0.5365 (7)	0.078
C42	0.2999 (5)	-0.2864 (11)	0.4497 (9)	0.086
C43	0.3384 (7)	0.5132 (11)	-0.0070 (8)	0.093
C44	0.5670 (7)	0.4238 (13)	0.1014 (10)	0.104
H 39A	0.07877	-0.55993	0.13947	0.083
H 39B	0.16647	-0.45803	0.17347	0.083
H 39C	0.10147	-0.48433	0.04387	0.083
H 29	-0.03229	-0.40410	0.19723	0.03 (1)
H 36A	-0.11584	-0.45225	0.00015	0.08 (2)
H 36B	-0.12884	-0.28375	-0.02485	0.12 (4)
H 36C	-0.18094	-0.35975	0.04625	0.09 (3)
H 9	-0.06988	0.01761	0.33220	0.03 (1)
H 11	-0.00588	-0.05294	0.52476	0.04 (2)
H 38A	0.02228	0.32087	0.25760	0.05 (2)
H 38B	-0.05082	0.27407	0.31250	0.07 (2)
H 38C	-0.05652	0.20227	0.19730	0.06 (2)
H 23A	0.15810	0.15298	0.26396	0.11 (3)
H 23B	0.08350	0.03018	0.20336	0.07 (2)
H 23C	0.16620	0.00018	0.32286	0.05 (2)
H 21	0.18025	0.35429	0.43612	0.05 (2)
H 30	0.27061	0.39451	0.63515	0.12 (4)
H 34	0.26150	0.22917	0.77327	0.06 (2)
H 26	0.15842	0.02405	0.71492	0.05 (2)
H 35	0.32665	-0.32987	0.30519	0.05 (2)
H 42	0.26801	-0.37741	0.44980	0.08 (2)
H 41	0.28828	-0.20455	0.59598	0.08 (2)
H 33	0.36335	0.02127	0.59629	0.08 (3)
H 25	0.49584	0.13518	0.50794	0.04 (1)
H 20	0.54516	0.04858	0.36533	0.04 (2)
H 32A	0.36472	-0.00174	0.10937	0.04 (2)
H 32B	0.29922	0.04046	0.17557	0.07 (2)

H 32C	0.29982	-0.12064	0.13357	0.08 (2)
H 40A	0.51605	-0.14890	0.20872	0.068
H 40B	0.45615	-0.27260	0.23572	0.068
H 40C	0.54165	-0.19930	0.33582	0.068
H 31	0.48145	0.45732	0.19296	0.05 (2)
H 44A	0.55439	0.51704	0.06306	0.09 (3)
H 44B	0.57339	0.35024	0.05026	0.10 (3)
H 44C	0.62569	0.42894	0.16846	0.12 (4)
H 43A	0.36109	0.60648	0.02998	0.086
H 43B	0.27489	0.50108	-0.00802	0.086
H 43C	0.33419	0.52418	-0.08472	0.086

Intramolecular bond length/Å (H omitted)

atom atom	distance	atom atom	distance
O1 --C11	1.467 (8)	O1 --C15	1.347 (7)
O2 --C15	1.196 (10)	N3 --C9	1.464 (9)
N3 --C12	1.397 (8)	N3 --C15	1.398 (9)
O4 --C12	1.193 (9)	O5 --C24	1.357 (10)
O5 --C25	1.478 (10)	O6 --C28	1.204 (10)
O7 --C24	1.202 (11)	C8 --C15	1.488 (10
C8 --C13	1.380 (9)	C8 --C26	1.394 (8)
C9 --C11	1.542 (8)	C9 --C14	1.568 (10)
N10 --C20	1.459 (10)	N10 --C24	1.399 (10)
N10 --C28	1.402 (9)	C12 --C29	1.523 (11)
C13 --C14	1.524 (8)	C13 --C21	1.390 (10)
C14 --C23	1.551 (9)	C14 --C38	1.523 (10)
C16 --C18	1.521 (9)	C16 --C22	1.384 (10)
C16 --C35	1.400 (11)	O17 --C27	1.201 (11)
C18 --C20	1.574 (10)	C18 --C32	1.534 (10)
C18 --C40	1.529 (11)	O19 --C37	1.210 (12)
C20 --C25	1.544 (9)	C21 --C30	1.406 (11)
C22 --C25	1.476 (11)	C22 --C33	1.395 (10)
C26 --C34	1.393 (12)	C27 --C29	1.519 (10)
C27 --C39	1.493 (13)	C28 --C31	1.518 (12)
C29 --C36	1.528 (10)	C30 --C34	1.393 (12)
C31 --C37	1.513 (11)	C31 --C44	1.539 (13)
C33 --C41	1.382 (14)	C35 --C42	1.389 (13)
C37 --C43	1.489 (14)	C41 --C42	1.402 (15)

Intramolecular bond angles/degrees (H omitted)

atom atom atom	angle	atom atom atom	angle
C11 --O1 --C15	110.8 (5)	C9 --N3 --C12	119.9 (6)
C9 --N3 --C15	111.8 (5)	C12 --N3 --C15	127.6 (7)
C24 --O5 --C25	111.4 (6)	C11 --C8 --C13	111.1 (5)
C11 --C8 --C26	127.4 (6)	C13 --C8 --C26	121.5 (7)
N3 --C9 --C11	101.7 (6)	N3 --C9 -C14	116.3 (5)
C11 --C9 --C14	107.9 (5)	C20 --N10 --C24	112.0 (6)
C20 --N10 --C28	120.3 (6)	C24 --N10 --C28	127.5 (7)
O1 --C11 --C8	112.3 (5)	O1 --C11 --C9	105.0 (5)
C8 --C11 --C9	105.2 (6)	N3 --C12 --O4	117.9 (7)
N3 --C12 --C29	117.8 (6)	O4 --C12 --C29	124.3 (6)
C8 --C13 --C14	113.1 (6)	C8 --C13 --C21	120.5 (6)
C14 --C13 --C21	126.4 (6)	C9 --C14 --C13	101.8 (5)
C9 --C14 --C23	112.8 (6)	C9 --C14 --C38	110.2 (5)
C13 --C14 --C23	108.4 (5)	C13 --C14 --C38	112.2 (6)
C23 --C14 --C38	111.1 (6)	O1 --C15 --O2	122.4 (6)
O1 --C15 --N3	109.2 (6)	O2 --C15 --N3	128.3 (6)
C18 --C16 --C22	112.9 (7)	C18 --C16 --C35	127.1 (7)
C22 --C16 --C35	119.9 (7)	C16 --C18 --C20	101.3 (5)
C16 --C18 --C32	109.9 (5)	C16 --C18 --C40	111.9 (7)
C20 --C18 --C32	112.9 (6)	C20 --C18 --C40	109.5 (6)
C32 --C18 --C40	111.0 (6)	N10 --C20 --C18	116.1 (5)
N10 --C20 --C25	101.8 (6)	C18 --C20 --C25	107.1 (6)
C13 --C21 --C30	118.4 (7)	C16 --C22 --C25	111.0 (6)
C16 --C22 --C33	121.8 (8)	C25 --C22 --C33	127.2 (7)
O5 --C24 --O7	124.1 (8)	O5 --C24 --N10	107.8 (7)
O7 --C24 --N10	128.0 (8)	O5 --C25 --C20	103.0 (5)
O5 --C25 --C22	111.6 (6)	C20 --C25 --C22	105.2 (6)
C8 --C26 --C34	118.7 (7)	O17 --C27 --C29	120.8 (8)
O17 --C27 --C39	122.7 (8)	C29 --C27 --C39	116.4 (7)
O6 --C28 --N10	118.3 (8)	O6 --C28 --C31	124.3 (7)
N10 --C28 --C31	117.5 (7)	C12 --C29 --C27	108.7 (6)
C12 --C29 --C36	109.7 (6)	C27 --C29 --C36	109.0 (6)
C21 --C30 --C34	121.0 (8)	C28 --C31 --C37	109.5 (7)
C28 --C31 --C44	110.6 (7)	C37 --C31 --C44	108.9 (7)
C22 --C33 --C41	118.2 (8)	C26 --C34 --C30	120.0 (7)
C16 --C35 --C42	118.7 (8)	O19 --C37 --C31	120.2 (8)
O19 --C37 --C43	121.5 (8)	C31 --C37 --C43	118.3 (8)
C33 --C41 --C42	120.7 (8)	C35 --C42 --C41	120.7 (9)

4. References and Notes

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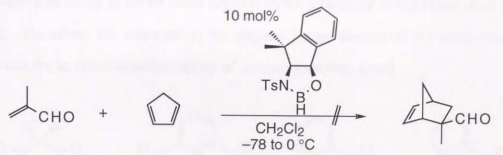
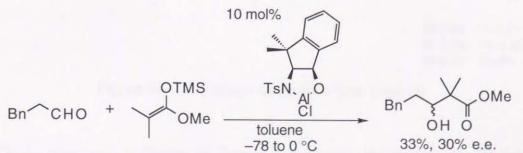
Section III. Application of *cis*-2-Amino-3,3-dimethyl-1-indanol as a Precursor of Chiral Catalysts

1. Introduction

As described in Chapter III, Section I and Section II, a novel artificial chiral amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol was synthesized, resolved, and applied as a precursor of a chiral oxazolidinone-type template. Then, the author next intended to apply this amino alcohol as a precursor of several chiral catalysts. First, the enantioselective Diels-Alder reaction and aldol reaction were examined using a boron and an aluminium catalyst, respectively, which were modified by *N*-Ts amino alcohol derived from **III-3** (Scheme III-29). However, these reactions were unsuccessful.

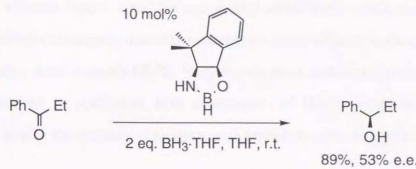
Scheme III-29



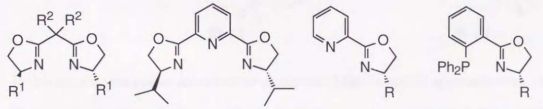


The enantioselective reduction of propiophenone using a chiral oxazaborolidine, which was prepared by mixing **III-3** and borane·THF complex, was also investigated, however much lower enantioselectivity was observed than that obserbed in the case using *cis*-2-amino-1-acenaphthenol-derived oxazaborolidine was used as a catalyst (Scheme III-30).

Scheme III-30



The author next intended to derive **III-3** into a ligand, which contains oxazoline moiety as a electron donner, and to apply it as a ligand for transition-metal catalyzed enantioselective reactions. Oxazoline-containing ligands can be easily synthesized from various homochiral amino alcohols and appropriately used for various catalytic enantioselective reactions (Fig. III-10).[1] Recently, 2-[*o*-(diphenylphosphino)phenyl]oxazoline **III-69** has been developed and applied as a ligand for various transition metal-catalyzed reactions by several groups.[2-6] The chiral induction ability of **III-69** much depends on the substituent at 4-position of its oxazoline moiety. Therefore, the structure of the original amino alcohol of the oxazoline is quite responsible for its chiral induction ability of the corresponding ligand.



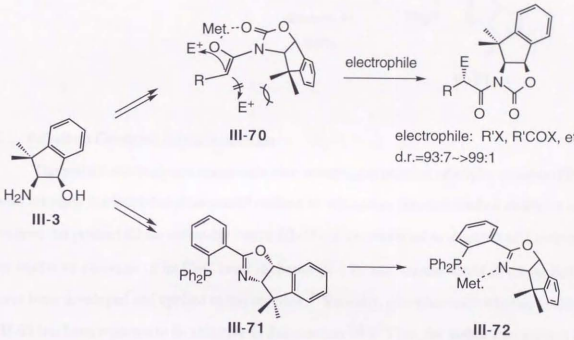
III-69a: R=*i*-Pr
III-69b: R=*t*-Bu
III-69c: R=Ph

Figure III-10. Various Oxazoline-type Ligands

On the other hand, in Chapter III, Section II, the author described that the **III-3**-derived chiral oxazolidinone was found to be a quite efficient chiral auxiliary in various diastereoselective reactions of the corresponding imide enolates (Scheme III-31). These successful results are considered to arise from the structural characteristic of **III-3**; the conformationally fixed two methyl substituents of **III-3** shield the one side of the diastereoface of the corresponding enolate **III-70** quite effectively. On the basis of this consideration, the

author expected that 2-[*o*-(diphenylphosphino)phenyl]oxazoline **III-71**, derived from **III-3**, would be an efficient ligand, since the two methyl substituents would similarly strongly influence the chiral environment near to the stereogenic center adjacent to the nitrogen atom of the corresponding metal complex **III-72**. Furthermore, since both enantiomers of **III-3** can be obtained easily via its resolution, both enantiomers of **III-71** would be available and appropriately used in the synthesis of products with desired absolute configurations.

Scheme III-31



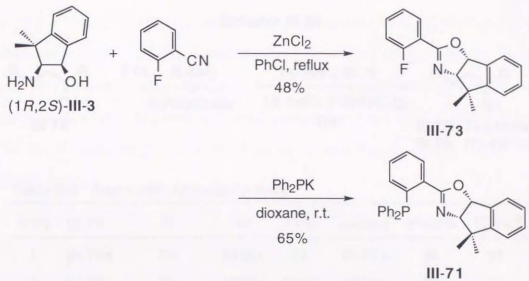
In this section, the author describes the synthesis of **III-71** and its applications as a chiral ligand for enantioselective palladium-catalyzed allylic amination reaction and rhodium-catalyzed hydrosilylation of ketones.

2. Results and Discussion

2.1. Synthesis of 2-[*o*-(Diphenylphosphino)phenyl]oxazoline **III-71**

III-71 was synthesized from **III-3** in two steps according to the reported procedure for preparing **III-69** (Scheme III-32).[2] Condensation of (1*R*,2*S*)-**III-3** with 2-fluorobenzonitrile in the presence of a catalytic amount of $ZnCl_2$ gave 2-(*o*-fluorophenyl)oxazoline **III-73**, which was successively treated with Ph_2PK to give **III-71**.

Scheme III-32



(1*R*,2*S*)-**III-3**

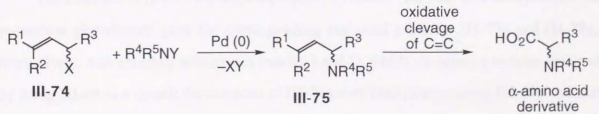
III-73

III-71

2.2. Palladium-Catalyzed Allylic Amination

The palladium-catalyzed enantioselective substitution reaction of allylic substrate **III-74** with nitrogen nucleophiles is an useful method to synthesize enantioenriched α-amino acid, because the product allylic amine derivative **III-75** can be converted to α-amino acid derivative by oxidative cleavage of its C=C bond (Scheme III-33), and various kinds of chiral ligands have been developed and applied to this reaction.[7] Recently, phosphorus-containing oxazoline **III-69** has been reported to be effective in this reaction.[3d-g] Thus, the author first applied **III-71** to the palladium-catalyzed enantioselective allylic amination reaction.

Scheme III-33



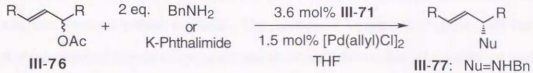
III-74

III-75

The reaction was carried out in THF using a catalyst prepared *in situ* by mixing 1.5 mol% of [Pd(allyl)Cl]$_2$ and 3.6 mol% of **III-71** (Scheme III-34, Table III-9). As nitrogen

nucleophiles, benzylamine and potassium phthalimide (2 equivalent to the substrate) were selected.

Scheme III-34



III-76

III-77: Nu=NHBn
III-78: Nu=NPhth

Table III-9. Asymmetric Amination of **III-76**

entry	**III-76**	R	Nu	temp.	product	yield/%	% e.e.[a]
1	**III-76a**	Ph	NHBn	r.t.	**III-77a**	89	97
2	**III-76a**	Ph	NPhth	50 °C	**III-78a**	88	99
3	**III-76b**	*p*-Cl-C_6H_4	NHBn	r.t.	**III-77b**	94	95
4	**III-76b**	*p*-Cl-C_6H_4	NPhth	50 °C	**III-78b**	81	98
5	**III-76c**	*p*-Br-C_6H_4	NHBn	r.t.	**III-77c**	66[b]	99
6	**III-76c**	*p*-Br-C_6H_4	NPhth	50 °C	**III-78c**	40[c]	97
7	**III-76d**	*o*-Br-C_6H_4	NHBn	reflux	–	0[d]	–
8[e]	**III-76e**	Me	NHBn	reflux	**III-77e**	80[f]	20[g]

[a] Determined by chiral HPLC analysis (Daicel Chiralcel OD). [b] **III-76c** was recovered in 22% yield. [c] **III-76c** was recovered in 54% yield. [e] 5 mol% $[Pd(allyl)Cl]_2$ and 12 mol% **III-71** were used. [d] **III-76d** was recovered almost quantitatively. [f] *E*:*Z* ratio of the product was determined to be 96:4 by 270 MHz ^{1}H-NMR analysis. [g] E.e of (*E*)-isomer determined by 270MHz ^{1}H-NMR analysis of the corresponding MTPA amide.

The reactions of (*E*)-1,3-diphenyl-2-propen-1-yl acetate (**III-76a**) with benzylamine and potassium phthalimide gave the corresponding aminated products **III-77a** and **III-78a**, respectively, with excellent selectivities (entries 1 and 2), which are superior to those obtained by using **III-69** as a ligand; the reactions of **III-76a** with benzylamine using **III-69b** and that with potassium phthalimide using **III-69a** gave **III-77a** of 89% e.e. and **III-78a** of 96% e.e., respectively; it is also reported that the reaction of methyl (*E*)-1,3-diphenyl-2-propen-1-yl carbonate with benzylamine using **III-69c** gave **III-77a** of 94% e.e.[3f,g] Excellent selectivities were observed also in the amination reactions of **III-76b** and **III-76c**, which

contain *para* substituted phenyl groups (entries 3 to 6). The reactions of **III-76c** did not completed, and that of **III-76d** did not proceeded. The reason for these unsatisfactory results is not clear at present, since no significant by-product, such as expected to be formed via oxidative addition of the palladium complex to the C-Br bond of the substrates or to the reaction products, was obtained in these reactions. The reaction of 3-penten-2-yl acetate (**III-76e**) with benzylamine required raising temperature and increasing the amount of the catalyst, and gave **III-77e** with disappointingly low enantioselectivity, which was presumably arised from high reaction temperature.

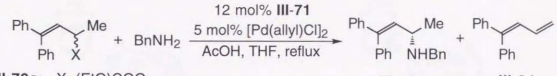
The absolute configuration of **III-77a** was confirmed to be *R* in comparison of its sign of the optical rotation with that in the literature.[3g] The absolute configurations of the other products are also confirmed to be *R* by correlation of the signs of their optical rotations (the signs of all the products are minus) and the elution order in HPLC analysis with those of **III-77a**.

Since the reaction of **III-77e** with benzylamine was unsuccessful, the author next investigated amination reaction of 1,1-diphenyl-3-buten-2-ol derivatives **III-79**, which is able to be regarded as an equivalent of **III-76e**, because the same alanine derivative can be obtained by oxidative cleavage of the C=C bonds of the products obtained by the amination reactions of **III-76e** and **III-79** (cf. Scheme III-33). Bosnich and his co-workers reported that the reaction of the acetate **III-79b** with benzylamine was catalyzed by the complex of palladium with chiral diphosphine to give the corresponding amine regioselectively with moderate enantioselectivity (up to 76% o.p.).[8] On the other hand, Williams and his co-workers reported that the reaction of **III-79b** with potassium phthalimide using **III-69**-palladium complex as a catalyst did not proceed.[3e]

The reaction of the carbonate **III-79a** with benzylamine gave the corresponding amine **III-80** with good enantioselectivity (Scheme III-35, Table III-10, entry 1). However, the yield of **III-80** was low, and a significant amount of 4,4-diphenyl-1,3-butadiene (**III-81**) was obtained. Utilization of the acetate **III-79b** as a substrate slightly improved both chemical yield and enantiomeric purity of **III-80**. On the basis of the result, the author supposed that acetic acid, which was gradually formed with the progress of the reaction, played a significant role in this reaction. Therefore, the author investigated the effect of addition of acetic acid. Addition

of acetic acid (2 eq. of **III-79b**) slightly enhanced the formation of **III-80**, and fortunately, also increased its enantiomeric purity (entries 3 vs 2). To the contrary, when 1-adamantylcarboxylic acid was added instead of acetic acid (entry 4), the formation of diene **III-81** was enhanced and the yield and enantiomeric purity of **III-80** were diminished. Addition of 5 eq. of acetic acid inhibited complete conversion of **III-79b**, which is supposed to be caused by decomposition of the ligand (entry 5). However, by increasing the amount of benzylamine from 2 eq. to 5 eq. as well as that of acetic acid, **III-80** was obtained in 79% yield with 98% e.e. (entry 6).

Scheme III-35



III-79a: X=(EtO)COO
III-79b: X=AcO

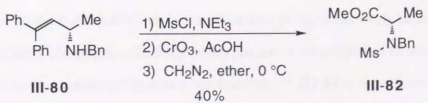
III-80 **III-81**

Table III-10. Effect of Addition of Acetic Acid in Asymmetric Amination of **III-79**

entry	III-79	amount of AcOH/eq.	amount of $BnNH_2$/eq.	yield/%		% e.e.
				III-80	III-81	of III-80[a]
1	**III-79a**	–	2	14	71	85
2	**III-79b**	–	2	38	54	92
3	**III-79b**	2	2	48	49	98
4[b]	**III-79b**	2	2	16	81	90
5	**III-79b**	5	2	43	36[c]	>99
6	**III-79b**	5	5	79	20	98

[a] Determined by chiral HPLC analysis (Daicel Chiralcel OJ).
[b] 1-Adamantylcarboxylic acid was added instead of acetic acid.
[c] **III-79b** was recovered in 21% yield.

Scheme III-36



III-80 **III-82**

According to the procedure reported by Bosnich and his co-workers, **III-80** was converted to methyl (–)589-(*S*)-2-(*N*-benzyl-*N*-mesylamino)propionate (**III-82**) (Scheme III-36).[8] The absolute configuration of **III-80** was determined to be *S* on the basis of the absolute configuration of **III-82**.

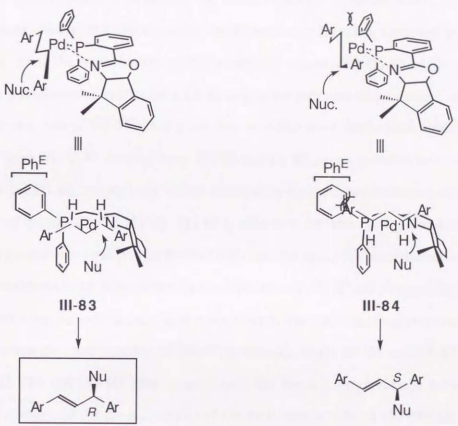


Figure III-11. Supposed Structures of π-Allylpalladium Intermediates

The excellent *R* selectivities in the reactions of **III-76** using **III-71**, which are superior to those obtained with using **III-69**, can be explained as follows. On the basis of the detailed NMR and X-ray crystallographic studies concerning the structure of the π-allylpalladium complex with **III-69a**,[6] the conformation of the diphenylphosphino group of the ligand is supposed to locate as shown in **III-83** and **III-84** (Fig. III-11). Since the nucleophilic attack of benzylamine to the π-allylpalladium intermediate occurs regioselectively at the carbon atom *trans* to phosphorus, the enantioselectivity of the product is considered to be strongly affected by the relative concentrations of these two intermediates.[6] **III-84** is more favorable than **III-85**, since the steric repulsion between Ar of π-allyl moiety and the equatorial phenyl group

(Ph^E) on the phosphorus atom in **III-85** is serious. When the ligand **III-71**, of which the conformationally fixed methyl substituents offer larger bulkiness than does *t*-butyl substituent of **III-69b**, was applied in these reactions, the π-allyl moiety is considered to be made more close to Ph^E in order to avoid the steric repulsion between the two methyl substituents of **III-71** and the π-allyl moiety. Therefore, the steric repulsion between R and Ph^E in **III-84** becomes more serious, and consequently, the formation of **III-84** is supposed to be strongly suppressed. Thus the benzylamine highly selectively reacts with **III-83** at the carbon atom *trans* to the phosphorus of intermediate **III-83** to give the products with excellent selectivities.

In the reaction of **III-79b**, there are four possible π-allylpalladium intermediates as shown in Figure III-12.[3e] Among them, **III-85** and **III-87** are supposed to be more favorable than **III-86** and **III-88**, respectively, on the basis of the similar consideration to that discussed in the case of the reaction of **III-76**. **III-85** is able to react with benzylamine at the carbon *trans* to the phosphorus to afford the product with resulted regio- and stereoselectivity, whereas **III-87** is considered to be responsible for the formation of (*R*)-**III-80** obtained by the reaction at the carbon atom *trans* to the nitrogen (even though this reaction is unfavorable, this is not negligible when the concentration of **III-87** increased). Since **III-85** and **III-87** are formed from (*S*)-**III-79b** and (*R*)-**III-79b**, respectively, the rapid interconversion between **III-85** and **III-87** is essential for the conversion of the both enantiomers of **III-79b** into (*S*)-**III-80** selectively (Fig III-13). The σ-allylpalladiums **III-89** and **III-90** would be the intermediates in such interconversions. Diene **III-81** is supposed to be formed by the β-elimination of palladium hydride from **III-90**. Therefore, the formation of a sufficient amount of **III-89** and **III-90**, along with the suppression of β-elimination of palladium hydride from **III-90**, is necessary to obtain (*S*)-**III-80** in high yield with excellent selectivity. From the contrary results obtained by the respective addition of acetic acid and 1-adamantylcarboxylic acid, the role of addition of carboxylic acids can be as follows. Since the bulkiness of acetate anion is small, it is able to strongly coordinate with palladium. Therefore, the formation of σ-allylpalladiums would be promoted by their stabilization upon fulfillment of the vacant sites of palladium (II) by acetate anions. Furthermore, the migration of the β-hydride to palladium (II) can be prevented by the coordination of acetate anions. To the contrary, 1-adamantylcarboxylic

acid is considered to be unable to coordinate to palladium because of its bulkiness, therefore, it only protonated benzylamine and reduced its nucleophilicity.

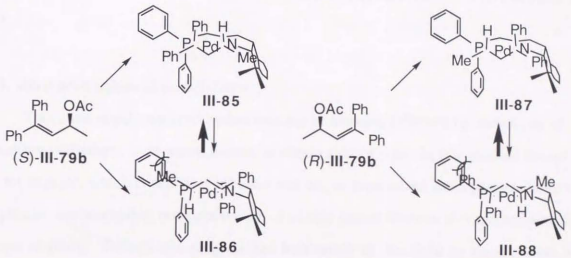


Figure III-12. Supposed Structures of π-Allylpalladium Intermediates

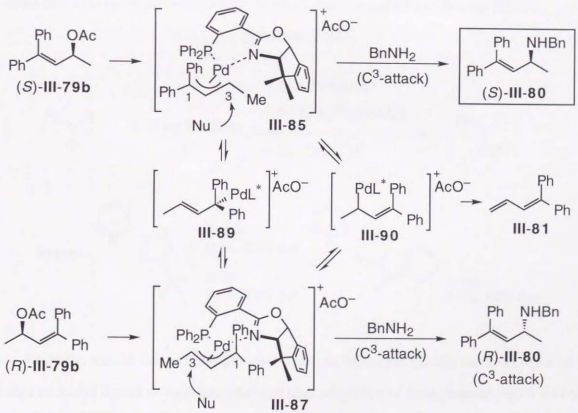


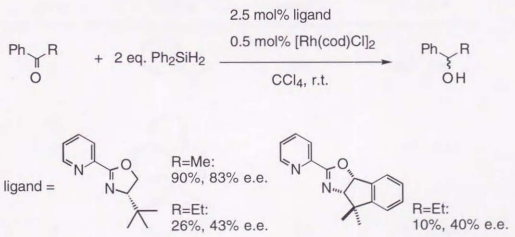
Figure III-13. Supposed Interconversions Between π-Allyl- and σ-Allylpalladium Intermediates

It is also possible that the diene **III-81** could be converted to the acetate **III-79b** which would be formed by palladium catalyzed addition of acetic acid. However, this mechanism can be excluded, since **III-81** was inert under the reaction conditions used in entry 6 in Table III-10.

2.3. Rhodium-Catalyzed Hydrosilylation

Transition metal-catalyzed hydrosilylation of ketones, followed by hydrolysis of the resulting silyl ethers, is an useful method to obtain alcohol, since in this reaction the use of metal hydride, which is sensitive to water and air, or pressurized hydrogen gas, which is explosive, can be avoided, and since the use of a chiral ligand allows to obtain enantioenriched chiral alcohols. Remarkable progress has been made in this field by development and application of ligands which contain nitrogen donners.[9] For example, 2-pyridyloxazoline derived from *t*-leucinol has been reported to be an efficient ligand. Stimulated by this result, the author intended to apply an analoguous ligand derived from *cis*-2-amino-3,3-dimethyl-1-indanol (**III-3**) to this reaction, however the result was unsatisfactory (Scheme III-37).

Scheme III-37



Recently, valinol-derived phosphorus-containing oxazoline **III-69a** has been reported to be also an useful ligand in rhodium-catalyzed hydrosilylation of acetophenone, but it was not applicable to hydrosilylation of other ketones such as α-tetralone because of the low selectivities.[4a,b] As mentioned above, the new phosphorus-containing oxazoline ligand **III-71**, derived from *cis*-2-amino-3,3-dimethyl-1-indanol (**III-3**), was found to be quite efficient

in the palladium-catalyzed amination reaction of various allyl alcohol derivatives. Encouraged by these successful results, the author next investigated the application of **III-71** as a ligand for the enantioselective rhodium-catalyzed hydrosilylation of ketones.

The reactions were carried out under the conditions, which Williams and his co-workers reported to be the best when valinol-derived ligand **III-69a** was used as a ligand (Scheme III-38).[4a] The results are listed in Table III-11. Hydrosilylation of dialkyl ketone gave the corresponding alcohol in moderate selectivity (entry 4), while hydrosilylation of aralkyl ketones gave the corresponding alcohols in good to excellent selectivity (entries 1 to 3), which are much superior to those obtained using **III-69** as a ligand.

Scheme III-38

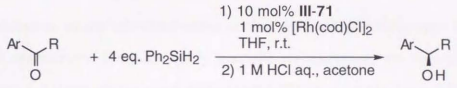


Table III-11. Enantioselective Hydrosilylation of Various Ketones

entry	ketone	yield/%	% e.e.[a]
1		92	92[b] (86)
2		77	93[b] (61)
3		73	86[b] (59)
4		81	48[c] (−)[d]

[a] The reported e.e. value obtained by using the valinol-derived ligand **III-69a** is given in the parenthesis. [b] Determined by chiral HPLC analysis (Daicel Chiralcel OB). [c] Determined by chiral HPLC analysis (Daicel Chiralcel OB) of the corresponding 2-naphthoate. [d] Not has been reported.

The absolute configurations of the product alcohols were all *R*, which are the same as expected on the basis of results of the case of **III-69a**.[4a] Therefore, the chiral induction mechanism for the reaction using **III-71** would be similar to that for the reaction using **III-69a**. Williams and his co-workers reported that **III-69a** (valinol-derived) is much more efficient ligand than **III-69b** (*t*-leucinol-derived).[4a] This result indicates that the selectivity is anti-proportional to the bulkiness of the substituent at the 4-position of the oxozoline moiety of the ligand. From the point of view of bulkiness, the chiral induction ability of **III-71** is anomalously excellent; the conformationally fixed two methyl substituents of **III-71** are considered to be more bulky than *t*-Bu substituent, of course, much more bulky than *i*-Pr substituent. In order to clarify the mechanism, the author has to carry out detailed studies concerning the structure of the Rh(I) complex of **III-71** and intermediates in the reaction.

In conclusion, an artificial chiral amino alcohol, *cis*-2-amino-3,3-dimethyl-1-indanol, of which both enantiomeric forms are easily available via resolution, was converted into the corresponding chiral phosphorus-containing oxazoline **III-71** and applied as a chiral ligand for transition metal-catalyzed enantioselective reactions. **III-71** was found to be a much more efficient ligand for palladium-catalyzed enantioselective allylic amination and rhodium-catalyzed enantioselective hydrosilylation of ketones than the similar ligands derived from valinol and *t*-leucinol.

3. Experimental

General information is same as that of Experimental in Chapter II, Section 1.

(3a*R*,8b*S*)-2-(2-Fluorophenyl)-3a,8b-dihydro-4,4-dimethyl-4*H*-indeno [1,2-*d*]oxazole (III-73). To a suspension of $ZnCl_2$ (30 mg) and (1*R*,2*S*)-2-amino-3,3-dimethyl-1-indanol (**III-3**) (556 mg, 3.14 mmol) in chlorobenzene (7 mL), was added 2-fluorobenzonitrile (0.38 g, 3.2 mmol). The mixture was stirred for 48 h with refluxing. The mixture was concentrated under reduced pressure and purified by column chromatography (hexane/ethyl acetate (20/1)) to give **III-73** as a greenish amorphous mass (420 mg, 1.49 mmol, 48%) which was used for the following reaction without further purification.

An analytical sample was recrystallized from hexane to give colorless prisms: mp 115-116 °C; $[\alpha]^{21.6}_{589}$ +120 (*c* 1.71, $CHCl_3$); IR (KBr) 1640, 1495, 1150; ^{1}H-NMR ($CDCl_3$) δ 1.06 (3H, s), 1.21 (3H, s), 4.41 (1H, d, *J*=7.6), 5.74 (1H, d, *J*=7.6), 7.0-7.9 (8H, m). Anal. Calcd for $C_{18}H_{16}FNO$: C, 76.85; H, 5.73; N, 4.98. Found: C, 76.63; H, 5.70; N, 4.94.

(3a*R*,8b*S*)-2-[2-(Diphenylphosphino)phenyl)-3a,8b-dihydro-4,4-dimethyl-4*H*-indeno[1,2-*d*]oxazole (III-71). To potassium diphenylphosphide (34 mL, 9.2 mmol; 0.27 M solution in THF/dioxane (4/6)) was added a solution of **III-73** (1.30 g, 4.62 mmol) in THF (5 mL) at 0 °C, and the resulting solution was stirred for 1 h at r.t. The reaction was quenched by adding water (30 mL), and the mixture was extracted with ether (3 × 20 mL). After the usual workup followed by purification by column chromatography (hexane/ethyl acetate (19/1)) gave **III-71** as a colorless amorphous mass (1.43 g, 3.19 mmol, 65%): $[\alpha]^{22.4}_{589}$ +94.8 (*c* 2.99, $CHCl_3$); IR (KBr) 1642; ^{1}H-NMR ($CDCl_3$) δ 1.08 (3H, s), 1.21 (3H, s), 4.50 (1H, d, *J*=7.6), 5.84 (1H, d, *J*=7.6), 6.8-6.9 (1H, m), 7.1-7.4 (16H, m), 7.8-7.9 (1H, m); HRMS(EI) calcd for $C_{30}H_{26}NOP$ 447.1752, found 447.1737.

Substrates for Palladium Catalyzed Allylic Amination.

(*E*)-1,3-Bis(2-chlorophenyl)-2-propenyl acetate (III-76b). To a suspension of (*E*)-1,3-bis(2-chlorophenyl)-1-oxo-2-propene (0.80 g, 2.9 mmol) and cerium chloride heptahydrate (1.1 g, 2.9 mmol) in methanol (20 mL), sodium borohydride (0.10 g, 2.9 mmol) was added in several portions at 0 °C. The reaction mixture was stirred at the same temperature for 10 min. The reaction was quenched by adding water (20 mL), and the mixture was extracted with ether (3 × 30 mL). The usual workup gave a viscous oil ((*E*)-1,3-bis(2-chlorophenyl)-2-propen-1-ol), which was used for the following reaction without further purification. To an ethereal solution of this alcohol (4 ml) was added pyridine (1 ml) and acetyl chloride (0.50 mL, 7.0 mmol) at 0 °C, and this mixture was stirred for 12 h. The reaction was quenched by adding water (10 mL), and the mixture was extracted with ether (3 × 20 mL). The combined extracts were washed with 10% HCl aq. (3 × 20 mL), saturated $NaHCO_3$ aq. (30 mL), and brine (30 mL). After the usual workup followed by purification by column chromatography (hexane/ethyl acetate (9/1)) gave **III-76b** as a colorless oil (0.93 g, 2.9 mmol,

quant.): IR (NaCl) 1740, 1230; ^{1}H-NMR ($CDCl_3$) δ 2.13 (3H, s), 6.27 (1H, dd, *J*=6.6, 16), 6.38 (1H, d, *J*=6.6), 6.56 (1H, d, *J*=16), 7.2-7.4 (8H, m); HRMS(EI) calcd for $C_{17}H_{14}Cl_2O_2$ 320.0371, found 320.0360.

(*E*)-1,3-Bis(2-bromophenyl)-2-propenyl acetate (III-76c). According to the procedure given for the preparation of **III-76b**, from (*E*)-1,3-bis(2-bromophenyl)-1-oxo-2-propene (2.50 g, 6.8 mmol), **III-76c** (2.6 g, 6.3 mmol, 93%) was obtained as a colorless oil: IR (NaCl) 1740, 1230; ^{1}H-NMR ($CDCl_3$) δ 2.13 (3H, s), 6.30 (1H, d, *J*=22), 6.30 (1H, dd, *J*=16, 22), 6.54 (1H, dd, *J*=16), 7.22 (2H, d, *J*=8.6), 7.27 (2H, d, *J*=8.6), 7.42 (2H, d, *J*=8.6), 7.50 (2H, d, *J*=8.6); HRMS(EI) calcd for $C_{17}H_{14}Br_2O_2$ 407.9360, found 407.9374.

Palladium Catalyzed Allylic Amination.

General Procedure for Substitution with Benzylamine. To $[Pd(allyl)Cl]_2$ (3.5 mg, 0.0096 mmol) and ligand **III-71** (10.6 mg, 0.0237 mmol) was added THF (1.0 mL), and the resulting solution was stirred for 20 min. To this solution was added a solution of allylic acetate **III-76** (0.634 mmol) in THF (1.0 mL) and a solution of benzyl amine (175 mg, 1.63 mmol) in THF (1.0 ml), successively. The mixture was stirred for 19-24 h at r.t. The mixture was concentrated under reduced pressure. The residue was purified by PTLC to give the corresponding amine as colorless oil. Chiral HPLC analysis of the product was performed in order to determine the enantioselectivity, for which purpose an authentic sample was prepared by reaction of **III-76** with benzylamine catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$/dppf (1/1).

(*R*)-*N*-Benzyl-[(*E*)-1,3-diphenyl-2-propenyl]amine (III-77a). The reaction of **III-76a** (160 mg, 0.634 mmol) for 19 h, followed by purification by PTLC (hexane/ethyl acetate (9/1)), gave **III-77a** (169 mg, 0.563 mmol, 89%) as a colorless oil. The e.e. was determined to be 97% by chiral HPLC analysis (Daicel Chiralcel OD, hexane/*i*-PrOH (199/1), α 1.13, shorter retention time for the *R* isomer): $[\alpha]^{25.6}_{589}$ –25.7 (*c* 1.68, $CHCl_3$) (lit. $[\alpha]^{20}_{589}$ –24.8 (*c* 1.4, $CHCl_3$) for the *R* isomer)[7b]; ^{1}H-NMR ($CDCl_3$) δ 1.70 (1H, s), 3.78 (1H, dd, *J*=13, 16), 4.39 (1H, d, *J*=7.3), 6.31 (1H, dd, *J*=7.3, 16), 6.58 (1H, d, *J*=16), 7.2-7.5 (15H, m).

(*R*)-*N*-Benzyl-[(*E*)-1,3-bis(2-cholorophenyl)-2-propenyl]amine (III-77b). The reaction of **III-76b** (204 mg, 0.634 mmol) for 21 h, followed by purification by PTLC

(hexane/ethyl acetate (9/1)), gave **III-77b** (220 mg, 0.598 mmol, 94%) as a colorless oil. The e.e. was determined to be 95% by chiral HPLC analysis (Daicel Chiralcel OD, hexane/*i*-PrOH (99/1), α 1.50, shorter retention time for the *R* isomer): $[\alpha]^{21.2}_{589}$ –7.3 (*c* 1.31, $CHCl_3$); IR (NaCl) 1490, 1190; ^{1}H-NMR ($CDCl_3$) δ 1.72 (1H, s), 3.74 (2H, s), 4.36 (1H, d, *J*=7.3), 6.22 (1H, dd, *J*=7.3, 16), 6.50 (1H, d, *J*=16), 7.2-7.4 (13H, m); HRMS(EI) calcd for $C_{22}H_{19}Cl_2N$ 367.0895, found 367.0885.

(*R*)-*N*-Benzyl-[(*E*)-1,3-bis(2-bromophenyl)-2-propenyl]amine (III-77c). The reaction of **III-76c** (260 mg, 0.634 mmol) for 24 h, followed by purification by PTLC (hexane/ethyl acetate (19/1)), gave **III-77c** (192 mg, 0.420 mmol, 66%) as a colorless oil. The e.e. was determined to be 97% by chiral HPLC analysis (Daicel Chiralcel OD, hexane/*i*-PrOH (99/1), α 1.40, shorter retention time for the *R* isomer): $[\alpha]^{25.6}_{589}$ –1.49 (*c* 8.44, $CHCl_3$); IR (NaCl) 1490; ^{1}H-NMR ($CDCl_3$) δ 1.65 (1H, br s), 3.74 (2H, s), 4.34 (1H, d, *J*=7.3), 6.23 (1H, dd, *J*=7.3, 16), 6.49 (1H, d, *J*=16), 7.2-7.6 (13H, m); HRMS(EI) calcd for $C_{22}H_{19}Br_2N$ 456.9863, found 456.9847.

General Procedure for Substitution with Pottasium Phthalimide. To a mixture of $[Pd(allyl)Cl]_2$ (3.5 mg, 0.0096 mmol), ligand **III-71** (10.6 mg, 0.0237 mmol), and potassium phthalimide (0.35 g, 1.9 mmol) was added THF (2.0 mL), and the resulting suspension was stirred for 20 min. To this solution was added a solution of allylic acetate **III-76** (0.636 mmol) in THF (1.0 mL). The mixture was stirred for 12 h at 50 °C. After cooling to r.t., the reaction was quenched by adding water (3 mL), and the mixture was extracted with ether (3 × 10 mL). After the usual workup and removal of the highly polar by-products by short column chromatography (hexane/ethyl acetate (1/1)), the mixture was purified by PTLC to give the corresponding *N*-phthalimide as colorless crystals. Chiral HPLC analysis of the product was performed in order to determine the enantioselectivity, for which purpose an authentic sample was prepared by reaction of **III-76** with benzylamine catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$/dppf (1/1).

(*R*)-*N*-[(*E*)-1,3-diphenyl-2-propenyl]-phthalimide (III-78a). The reaction of **III-76a** (161 mg, 0.636 mmol), followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-78a** (133 mg, 0.393 mmol, 79%) as a colorless oil. The e.e. was determined to be 99% by chiral HPLC analysis (Daicel Chiralcel OD, hexane/*i*-PrOH (99/1), α 1.29,

longer retention time for the *R* isomer): mp 119-120 °C; $[\alpha]^{25.6}_{589}$ –17.3 (*c* 1.70, $CHCl_3$); IR (KBr) 1710, 1385; HRMS(EI) calcd for $C_{23}H_{17}NO_2$ 339.1259, found 339.1261. Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.05; H, 5.21; N, 4.26.

(*R*)-*N*-[(*E*)-1,3-bis(2-cholorophenyl)-2-propenyl]-phthalimide (III-78b). The reaction of **III-76b** (204 mg, 0.634 mmol), followed by purification by PTLC (hexane/ethyl acetate (4/1)), gave **III-77b** (220 mg, 0.598 mmol, 94%) as a colorless oil. The e.e. was determined to be 95% by chiral HPLC analysis (Daicel Chiralcel OD, hexane/*i*-PrOH (599/1), α 1.48, longer retention time for the *R* isomer): mp 144-145 °C; $[\alpha]^{25.6}_{589}$ –14.0 (*c* 2.07, $CHCl_3$); IR (KBr) 1710, 1490, 1380; ^{1}H-NMR ($CDCl_3$) δ 6.07 (1H, d, *J*=8.6), 6.64 (1H, d, *J*=16), 6.97 (1H, dd, *J*=8.6, 16), 7.3-7.5 (8H, m), 7.7-7.9 (4H, m); HRMS(EI) calcd for $C_{23}H_{15}Cl_2NO_2$ 407.0479, found 407.0486. Anal. Calcd for $C_{23}H_{15}Cl_2NO_2$: C, 67.66; H, 3.70; N, 3.43. Found: C, 67.43; H, 3.77; N, 3.40.

(*R*)-*N*-[(*E*)-1,3-bis(2-bromophenyl)-2-propenyl]-phthalimide (III-78c). The reaction of **III-76c** (261 mg, 0.636 mmol), followed by purification by PTLC (hexane/ethyl acetate (9/1)), gave **III-78c** (126 mg, 0.254 mmol, 40%) as a colorless oil. The e.e. was determined to be 97% by chiral HPLC analysis (Daicel Chiralcel OD, hexane/*i*-PrOH (199/1), α 1.19, longer retention time for the *R* isomer): mp 89-90 °C; $[\alpha]^{25.6}_{589}$ –10.7 (*c* 1.20, $CHCl_3$); IR (KBr) 1710, 1490, 1380; ^{1}H-NMR ($CDCl_3$) δ 6.05 (1H, d, *J*=8.3), 6.63 (1H, d, *J*=16), 6.98 (1H, dd, *J*=8.3, 16), 7.2-7.5 (8H, m), 7.7-7.9 (4H, m); HRMS(EI) calcd for $C_{23}H_{15}Br_2NO_2$ 496.9419, found 496.9411.

(*S*)-*N*-Benzyl-(3,3-diphenyl-1-methyl-2-propenyl)amine (III-80). To a solution of $[Pd(allyl)Cl]_2$ (5.8 mg, 0.0159 mmol) and ligand **III-71** (17.8 mg, 0.0398 mmol) in THF (0.75 ml) was added a solution of acetate **III-79b** (83.0 mg, 0.312 mmol) and benzyl amine (175 mg, 1.63 mmol) in THF (1.0 ml), and was added AcOH (93.5 μl, 1.63 mmol). The mixture was stirred for 2 h with refluxing. After cooling to 0 °C, the reaction mixture was added 1 M NaOH aq. (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). After the usual workup and removal of the highly polar by-products by short column chromatography (hexane/ethyl acetate (1/1)), the mixture was purified by PTLC (hexane/ethyl acetate (9/1)) to give **III-80** as a colorless oil (77.7 mg, 0.248 mmol, 79%). The e.e. was determined to be 98% by chiral HPLC analysis (Daicel Chiralcel OJ, hexane/*i*-PrOH=9:1)) of

the product, for which purpose an authentic sample was prepared by reaction of **III-79b** with benzylamine catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$/dppf (1/1). The configuration of **III-80** was determined to be *S*, after its derivation into methyl 2-(*N*-benzyl-*N*-mesylamino)propionate according to the reported procedure.

(*S*)-Methyl-2-(*N*-benzyl-*N*-mesylamino)propionate (III-82). To a stirred solution of **III-80** 157 mg, 0.500 mmol) and triethylamine (0.3 mL) in CH_2Cl_2 (5 mL) added dropwise mesyl chloride (0.15 mL) at –20 °C. The resulting solution was stirred for 1 h at r.t. The reaction was quenched by adding water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). After usual workup of the extracts, purification by PTLC (hexane/ethyl acetate (3:1)) gave a viscous oil ((*S*)-*N*-Benzyl-(3,3-diphenyl-1-methyl-2-propenyl)-methanesulfonamide, 179 mg, 0.457 mmol, 91%).

To a solution of the above sulfonamide (179 mmol, 0.457 mmol) in acetic acid (2 mL) was added a solution of CrO_3 (0.30 g) in water (0.3 mL) at 0 °C. The resulting solution was stirred for 5 h at the same temperature. After adding water (10 mL), the reaction was extracted with ether (3 × 10 mL). Usual workup of the extracts gave the crude product mixture, which was treated with excess ethereal CH_2N_2. After quenching the reaction by adding acetic acid, followed by concentration of the mixture under reduced pressure, the resulting crude product were purified by PTLC (hexane/ethyl acetate (3/1)) to give the titled compound (54.2 mg, 0.200 mmol, 40% based on **III-82**): $[\alpha]^{25.6}_{589}$ –41.2 (*c* 2.24, $CHCl_3$) (lit. $[\alpha]_{589}$ +43.21 (c 1.6, $CHCl_3$) for the *R* isomer).[8]

Rhodium Catalyzed Hydrosilylation.

General Procedure. To a mixture of $[Rh(cod)Cl]_2$ (6.2 mg, 0.013 mmol), ligand **III-71** (56.0 mg, 0.125 mmol) was added THF (0.5 mL), and the resulting solution was stirred for 30 min. To this solution was added a solution of ketone (1.25 mmol) in THF (1.0 mL). Then Ph_2SiH_2 (1.0 ml, 5.0 mmol) was added at –78 °C and the resultant solution was stirred at r.t. for 24 h. After cooling to 0 °C, the reaction was quenched by adding 1M HCl aq. (3 mL) and acetone (5 ml). The mixture was stirred for 2 h and was extracted with ether (3 × 10 mL). After the usual workup, the mixture was purified by bulb-to-bulb distillation or column chlomatography to give the corresponding alcohol. The e.e. of the product alcohol was

determined by chiral HPLC analysis. The absolute configuration of the product alcohol was determined by a comparison of its retention time of chiral HPLC analysis with that of the authentic sample with known configuration, or a comparison of its sign of the optical rotation with that in the literature.

(*R*)-1-Phenylethanol. The reduction of acetophenone (156 mg, 1.25 mmol) according to the general procedure and purification by bulb-to-bulb distillation (ot 150 °C, 40 mmHg) gave 146 mg of the titled compound (1.20 mmol, 92%), of which absolute configuration and enantiomeric purity were determined to be *R* and 95% e.e., respectively, by chiral HPLC analysis (Daicel Chiralcel OB, hexane/2-propanol (15:1), α 1.59, longer retention time for the *R* isomer).

(*R*)-1-(1-Naphthyl)ethanol. The reduction of 1-acetonaphthone (225 mg, 1.25 mmol) according to the general procedure, and purification by PTLC ($CHCl_3$) gave 174 mg of the titled compound (1.01 mmol, 77%), of which absolute configuration and enantiomeric purity were determined to be *R* and 93% e.e., respectively, by chiral HPLC analysis (Daicel Chiralcel OB, hexane/2-propanol (15:1), α 1.25, longer retention time for the *R* isomer).

(*R*)-1,2,3,4-Tetrahydro-1-naphthol. The reduction of α-tetralone (183 mg, 1.25 mmol) according to the general procedure, and purification by PTLC (hexane/ethyl acetate (3/1)) gave 128 mg of the titled compound (0.866 mmol, 73%), of which absolute configuration and enantiomeric purity were determined to be *R* and 86% e.e., respectively, by chiral HPLC analysis (Daicel Chiralcel OB, hexane/2-propanol (15:1), α 2.60, shorter retention time for the *R* isomer).

(*R*)-Decan-2-ol. The reduction of 2-decanone (195 g, 1.25 mmol) according to the general procedure gave 0.16 g of the crude titled compound, which was successively treated with 2-naphthoyl chloride (5 eq.) and an excess amount of pyridine. The reaction was quenched by adding 1M HCl aq. Extraction of the mixture with ether (3×10 mL) followed by usual workup gave the corresponding 2-naphthoate of the titled compound (316 mg, 1.01 mmol, 81%) of which enantiomeric purity was determined to be 48% e.e. by chiral HPLC analysis (Daicel Chiralcel OB, hexane, α 2.60, shorter retention time for the *R* isomer).

4. References and Notes

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LIST OF PUBLICATIONS

1. Original Papers

(1) The Chiral Amino Alcohol, *cis*-2-Amino-1-acenaphthenol: Synthesis, Resolution, and Application to the Diastereoselective [2,3]-Wittig Rearrangement
Sudo, A.; Hashimoto, Y.; Kimoto, H; Hayashi, K.; Saigo, K.
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(2) *cis*-2-Amino-1-acenaphthenol: Practical Resolution and Application to the Catalytic Enantioselective Reduction of Ketones
Sudo, A.; Matsumoto, M.; Hashimoto, Y.; Saigo, K.
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(3) *cis*-2-Amino-3,3-dimethyl-1-indanol: Synthesis, Resolution, and Application as a Highly Efficient Chiral Auxiliary
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(4) Design, Synthesis, Resolution, and Application of a Highly Efficient Artificial Chiral Auxiliary: *cis*-2-Amino-3,3-dimethyl-1-indanol
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(5) *cis*-2-Amino-3,3-dimethyl-1-indanol: Application as a Highly Efficient Chiral Auxiliary for the Diels-Alder Reaction
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Chem. Lett. **1997**, 97.

(6) New Phosphorus-containing Oxazoline Derived from *cis*-2-Amino-3,3-dimethyl-1-indanol: Application as a Highly Efficient Ligand to Transition Metal-catalyzed Enantioselective Reactions

Sudo, A.; Yoshida, H.; Saigo, K.

submitted for publication.

2. Related Papers

(1) Diastereoselective Synthesis of β-Amino Esters by the Lewis Acid-Mediated Reaction of *N*-Tosyl Aldimines with Ketene Bis(trimethylsilyl) Acetals

Shimada, S.; Saigo, K.; Abe, M.; Sudo, A.; Hasegawa, M.

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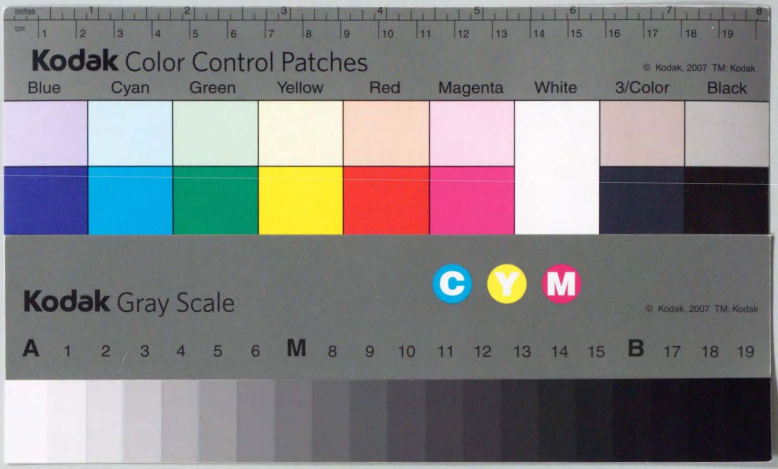
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